PB81-129207

Public Health Effects from Industrial Amines Production, A Preliminary Evaluative Approach. Volume I

PEDCo-Environmental, Inc.
Cincinnati, OH

Prepared for

Industrial Environmental Research Lab.
Research Triangle Park, NC

Nov 80

U.S. Department of Commerce
National Technical Information Service
NTIS.

IERL-RTP-1106

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/7-80-174a	2.
3. RECIPIENT'S ACCESSION NO. PB81 129207	
4. TITLE AND SUBTITLE Public Health Effects from Industrial Amines Production, a Preliminary Evaluative Approach; Volume 1	5. REPORT DATE November 1980 Issuing Date.
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) T. Briggs, M. Karaffa, and C. Sawyer (PEDCo); and P. Spaite (Consultant)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS PEDCo Environmental, Inc. 11499 Chester Road Cincinnati, Ohio 45246	10. PROGRAM ELEMENT NO. C2GN1E
	11. CONTRACT/GRANT NO. 68-02-2603 (Task 7) and 68-02-2149
12. SPONSORING AGENCY NAME AND ADDRESS EPA, Office of Research and Development Industrial Environmental Research Laboratory Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED Task Final; 6/77-4/79
	14. SPONSORING AGENCY CODE EPA/600/13

15. SUPPLEMENTARY NOTES IERL-RTP project officer is John O. Smith, Mail Drop 60, 919/541-2921.

16. ABSTRACT The report gives results of a study to assess the degree to which available data on health effects of chemical exposure, data from the National Cancer Institute, and information on production and use of classes of chemicals suspected of being carcinogenic might be used to identify possible cancer-related operations needing field investigation. The search for exposure intensity data confirmed that such data is not available from the open literature. Although published data are available on national production of some large-volume chemicals, site-specific data on such things as production rates, process losses, and process discharges are almost completely lacking. Until better sources of information are available, studies such as this will have to be supplemented with considerable field investigation to identify specific operations that are suitable for in-depth study. Until some way is established to develop such information so that it can be used with existing health data for identification of potential hazards, kepone and vinyl chloride incidents will continue to be dealt with after considerable damage has already been done. The data analysis techniques presented can be useful in identifying process discharges that must be studied in detail for definition of their potential environmental impact. Volume 2 of the report contains five appendices, including a list of industrial amine chemicals.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Pollution	Pollution Control	13B
Amines	Stationary Sources	07C
Carcinogens	Nitrosamines	
Epidemiology	Health Effects	13H
Nitroso Compounds		06E
Industrial Processes		06F
Public Health		
Environmental Biology		

18. DISTRIBUTION STATEMENT Release to Public	19. SECURITY CLASS *(This Report)* Unclassified	21. NO. OF PAGES 127
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (9-73)

PB81-129207

EPA-600/7-80-174a
November 1980

PUBLIC HEALTH EFFECTS FROM INDUSTRIAL AMINES PRODUCTION, A PRELIMINARY EVALUATIVE APPROACH

VOLUME 1

T. Briggs, M. Karaffa, C. Sawyer
PEDCo Environmental, Inc.
Cincinnati, Ohio 45246

Contract No. 68-02-2603
Assignment No. 7

P. Spaite
Paul W. Spaite Consultants
Cincinnati, Ohio

Contract No. 68-02-2149

Project Officer

John O. Smith

Project Manager

Joseph A. McSorley

Industrial Environmental Research Laboratory
Office of Research and Development
U.S. ENVIRONMENTAL PROTECTION AGENCY
Research Triangle Park, North Carolina 27711

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

This report was furnished to the U.S. Environmental Protection Agency by PEDCo Environmental, Inc., Cincinnati, Ohio, in fulfillment of Contract No. 68-02-2603, Task No. 7. The contents are reproduced herein as received from the contractor. The opinions, findings, and conclusions expressed are those of the authors and not necessarily those of the Environmental Protection Agency.

CONTENTS

	Page
Figures	v
Tables	vi
Acknowledgement	viii
1. Introduction	1
2. Project Overview	2
3. Results	6
4. Conclusions	18
5. Recommendations	21
6. Health Effects Assessment of Amines	22
6.1 Acute Toxicity and Noncarcinogenic Forms of Chronic Toxicity	24
6.2 Carcinogenicity	27
6.3 Historical Epidemiological of Aromatic Amines	34
6.4 Epidemiological Evidence Linking Individual Aromatic Amines with Human Carcinogensis	37
References	42
7. Health Effects Assessment of Nitrosamines	46
7.1 Acute Toxicity	48
7.2 Carcinogenicity	51
7.3 Synergistic Effects	60
7.4 Human Health Hazard	61
7.5 Mutagenicity and Teratogenicity	62
7.6 Epidemiology of Nitrosamines	63
References	67
8. Identification of Potentially Hazardous Commercially Significant Amines	70
8.1 Master List of Commercial Amine Products	70
8.2 Subset List of Potentially Hazardous Amine Chemicals	71
8.3 Selection of Sites for Investigation	77
References	88

CONTENTS (continued)

		Page
9.	Retrospective Epidemiological Analysis	89
	9.1 Selection of Cancer Types for Study	89
	9.2 General Methodology	90
	9.3 Epidemiological Analysis of Industrial Amines	92
	9.4 Cancer Mortality Relative to Contiguous County Levels	95
	9.5 Absolute Cancer Rate Comparison	98
	9.6 Cancer Mortality Relative to National Levels	98
	9.7 Population and Industrialization Data	102
	9.8 Facilities Producing Precursors for Nitrosamines	104
10.	Sources and Exposure of Amines and Nitrosamines	108
	10.1 Sources of Amines and Nitrosamines	108
	10.2 Eventual Environmental Levels	111
	10.3 Fate and Effects Analyses	111

FIGURES

No.		Page
6-1	Scheme for Metabolic Activation of Aromatic Amines	29
6-2	Development of Bladder Tumors Amount 503 Workers, 1960-68	38
7-1	Transformation of Nitrosamine to an Active Carcinogen	56
7-2	Metabolic Activation (left side) and Detoxification (right side) of N,N'-dialkylinitrosamines	57
10-1	Information Flow for Environmental Assessment of Amine Distribution and Effects	109
10-2	Overall Information Flow for Amine Fate and Effects Analysis	114

TABLES

No.		Page
3-1	Relative Rates of all Cancers Versus Selected Cancers in Thirteen Counties	7
3-2	Absolute Rates of all Cancers and Selected Cancers in Thirteen Counties	9
3-3	Thirteen-county Ranking Based on Relative Risk of all Cancers	11
3-4	Thirteen-county Ranking Based on Relative Risk and Adjusted Relative Risk of Bladder Cancer	12
3-5	Thirteen-county Population and Industrialization Data	14
3-6	Comparison of Five Selected Counties with Seven Counties with Highest National Rates of Cancer	16
6-1	Carcinogenicity of Some Aromatic Amines	32
6-2	Aromatic Amines for which Carcinogenicity or a Strong Suspicion of Carcinogenicity to Man Has Been Found	41
7-1	Acute Toxicity of Some N-Nitroso Compounds	49
7-2	Carcinogenicity of N-Nitroso Compounds in Rats	52
7-3	Localization of Tumors Induced by N-Nitroso Compounds in Rats	52
7-4	Sites of Tumors Produced by Some N-Nitroso Compounds	54
7-5	N-Nitroso Compounds and Related Substances Inducing Tumors Following Transplacental Exposure	59
8-1	Industry Categories of Classified Industrial Amine Chemicals	72
8-2	List of High Volume Industrial Amines	73

TABLES (continued)

No.		Page
8-3	List of Amine Derivative Chemicals With Possible Adverse Health Effects	75
8-4	Carcinogenic Amines Listed in the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man	78
8-5	Environmentally Hazardous Industrial Amine Compounds	79
8-6	Environmentally Hazardous Industrial Amines List Comparison With Other Published or Developed Lists	82
8-7	Amine Chemicals and Long-term Manufacturers	85
8-8	Results of Site Verification Contacts	86
9-1	List of Terms Associated With Cancer Incidence	94
9-2	Relative Rate of Selected Cancers for the Thirteen Counties	96
9-3	Summary of Population Distribution for Contiguous County Evaluation	97
9-4	Absolute Cancer Rates for All Cancers, Selected Cancers, and Bladder Cancer	99
9-5	All Cancer Rates and Relative Risk Data For Selected Cancers	100
9-6	Fourteen-county Ranking Based on National Averages/All Cancer Rates	103
9-7	Cancer Mortality Risks for the 20 Highest Counties Nationally	105
10-1	Drugs, Pesticides, and Naturally Occurring Amines That Have Experimentally Produced N-Nitroso Compounds in Vivo or in Vitro	112
10-2	Nitrosamine Concentrations in Ambient Air Measured in 12 U.S. Cities or Locatalities	113 in

ACKNOWLEDGMENT

This report was furnished to the U.S. Environmental Protection Agency by PEDCo Environmental, Inc., Cincinnati, Ohio. Charles J. Sawyer was the PEDCo Project Manager and Timothy Devitt functioned as Service Director. Principal authors of the report were Terry Briggs, Mark Karaffa, and Charles J. Sawyer of PEDCo and Paul W. Spaite, consultant.

John O. Smith was the Task Officer for the U.S. Environmental Protection Agency.

PUBLIC HEALTH EFFECTS FROM INDUSTRIAL AMINES PRODUCTION
A PRELIMINARY EVALUATIVE APPROACH

The objective of this study was to determine how far information in the open literature can be used as an inexpensive means of identifying industrial operations that appear to warrant costly characterization studies aimed at full definition of their potential impacts. Amine production was used as a model industrial activity because it has been established that cancer is produced in workers exposed to certain amines. The study was unsuccessful in relating excessive cancer rates in counties in which certain amines were manufactured. The study did, however, identify locations at which more extensive studies could be pursued. One of the main limitations of the study was the impossibility of determining amine exposure in the general population surrounding amine production facilities.

1.0 INTRODUCTION

In the last several years the priorities of the U.S. Environmental Protection Agency have shifted to detection and control of human and environmental exposures to toxic emissions containing carcinogenic materials. Chemical analysis and bioassay testing methods are being developed and used as valuable tools in this effort. It seems clear, however, that some systematic but inexpensive approach is needed to set priorities for industries to be investigated and discharge streams to be tested. This is expecially true for industries as complex as those involved with the production and use of synthetic organic chemicals.

Because it is felt that production and use of organic chemicals may be in some way relatable to more frequent occurance of some types of cancer this project was undertaken. Its purpose is to assess the degree to which available data on health effects of chemical exposure, data from the National Cancer Institute (NCI), and information on production and use of classes of chemical compounds suspected of being carcinogenic might be used to identify possible cancer-related operations needing further investigation in the field.

2.0 PROJECT OVERVIEW

It has been established that industrial usage of certain amine chemicals has in the past resulted in cancer in exposed workers. It also appears that operations involving amine chemicals may be contributing to atmospheric nitrosamines, which according to laboratory animal studies, are highly potent carcinogens. Hence industrial practices involving amines were selected for use in this investigation to define how far information in open literature can be used as an inexpensive means of identifying operations that appear to warrant costly characterization studies aimed at full definition of their potential impacts.

The main elements of the investigation were as follows:

1) A master list of over 1900 amine chemicals was developed using the Tariff Commission report on synthetic organic chemical production and the Stanford Research Institute Directory of Chemical Producers. These chemicals were divided into two groups: primary amines, which would not react with NO_x in the atmosphere to form nitrosamines, and secondary or tertiary amines, which could react.

2) Health effects literature was reviewed to identify studies that have been conducted to relate exposure of amines or nitrosamines to the incidence of cancer.

3) Using information from the study of commercial amines and background information from a health effects investigation, a list of 48 amine compounds were identified as candidates for more detailed study. Consideration was given to a) potential toxicity or carcinogenicity of the compound, b) volume of annual production (high

volume production was used as an index of possible exposure to humans), and c) potential for reaction to form toxic chemicals.

4) The Stanford Research Institute Directory of Chemical Producers was used to locate sites where one or more of the amines selected for study were being manufactured, and Moody's Industrial Directory was used to identify sites where it could be established that they had been produced for 25 years or longer. No attempt was made to be exhaustive in locating such sites. Investigation of 32 chemicals led to identification of 12 sites. One additional county, where amines have been used in large quantities for many years, was added to make a total of 13 considered suitable for further study.

5) The 13 counties selected were examined to determine the following:

   a. Whether secondary and tertiary amines capable of being converted to nitrosamines in the atmosphere were included in the population of amines being produced.

   b. Whether organic dyes and pigment in which amines are used were produced in any of the counties.

   c. Whether nitric acid plants, which might contribute to the conversion of amines to nitrosamines in the atmosphere, were present in any of the counties.

6) Data from the National Cancer Institute were used to examine cancer rates in two ways. First, rates of cancer in counties contiguous with those being investigated were compared with gates in the counties of interest. This approach was used to screen out the effect of local conditions (e.g., drinking water) that might be contributing to high incidence of cancer. Second, the absolute values for incidence of cancer were determined for those counties with high relative cancer rates.

7) The relative rates of all 14 kinds of cancer shown in the NCI data base were analyzed, giving special attention to six kinds believed most likely to be associated with amine or nitrosamine exposure (esophagus, stomach, liver, pancreas, kidney, and bladder). In addition the rates of all cancers were compared to provide an index of the general prevalance of cancer from all causes; and the rate for lung cancer, which is the dominant form in terms of frequency, was used as a basis for comparison of frequency of occurrence. A third index, the "relative risk" factor defined by the N.C.I., was used along with relative rates and absolute rates to rank the 13 counties.

8) Information was assembled on factors that might explain observed cancer rates (relative or absolute). This material included background on population, degree of industrialization, and types of chemical plants in operation in the 13 selected counties and all surrounding counties. The most notable factor not accounted for was age adjustment of the cancer rates observed, i.e., it was not possible to determine whether some of the higher rates could be attributable to generally older populations in some counties.

9) Concurrent with the epidemiological analysis, an attempt was made to obtain information on potential for human exposure to amines or nitrosamines resulting from production or use of chemicals in the selected counties.

The balance of the report presents, in varying degrees of detail, the results of these activities. Sections 4 and 5 present, as concisely as possible, what are considered the important results, conclusions, and recommendations. Section 6 through 10 and the Appendices present the background on analysis. Sections 6 and 7 discuss health effects studies; Sections 8 presents the background on the commercially significant amines; and Section 9 discusses the analysis of cancer rates.

An attempt is made to make the information comprehensive enough so that interested parties can review it independently and so that it can serve as a basis for further investigation of the role of industrial amine chemicals in the environment.

3.0 RESULTS

Specific sources of escape of amines to the environment could not be identified, and "intensity of exposure" data were not available within the scope of the study. Data are generally very sparse, even on something as basic as annual production rates at individual sites. Limited data are available on discharges from production and consumptive processes, and air quality information on atmospheric amines or nitrosamines is not available for any of the counties investigated. It was hoped that some useful information could be developed, even if it were in the form of total volume of each type of amines produced and/or consumed in each county, but unfortunately even such basic information could not be obtained. This precluded development of an environmental fate and effects analysis incorporating the epidemiology analysis initially planned. As a result, some interesting observations are less meaningful than they might have been had they been confirmed by some evidence of possible human exposures to significant amounts of amines or nitrosamines.

Table 3-1 presents the relative rates of all cancers versus selected cancers, and Table 3-6A presents the key for numbers and symbols used in the "Cancer profile comments" column in Tables 1 through 6. The relative rate is the ratio of the cancer rate for the county being investigated to the average rate for all surrounding counties. When high relative rates are observed along with high absolute rates, the high relative rate suggests that local factors do not account for the observed high frequency of cancer. Most of the counties in which relative rates are high for all cancers also have high relative rates for selected cancers. Washington County, Alabama, presents a notable exception

Table 3-1. RELATIVE RATES OF ALL CANCERS VERSUS SELECTED CANCERS IN THIRTEEN COUNTIES

All cancers				Selected cancers				Cancer profile comments[a]
County/state	Relative rate			County/state	Average relative rate			
	M	F	OA		M	F	OA	
Kanahwa, W. Va.	118	111	114	Kanahwa, W. Va.	140	111	128	(1) (2)
Erie, N.Y.	120	107	114	Erie, N.Y.	125	121	124	(1) (2)
Vigo, Ind.	116	108	112	Vigo, Ind.	119	114	116	(1) (2)
Harris, Tex.	106	108	106	Salem, N.J.	112	110	115	(1) (2)
Warren, N.J.	105	108	106	Washington, Ala.	78	152	97	(2)
St. Clair, Ill.	101	102	102	Harris, Tex.	106	104	104	(1) (2)
Salem, N.J.	98	105	100	Warren, N.J.	99	110	104	(1) (2)
Summit, Ohio	94	97	95	St. Clair, Ill.	96	95	99	(1)
St. Charles, La.	91	99	95	Brazoria, Tex.	92	93	93	
St. Louis, Mo.	91	96	94	Summit, Ohio	92	93	92	
Somerset, N.J.	89	92	91	Somerset, N.J.	88	97	91	
Brazoria, Tex.	87	92	90	St. Louis, Mo.	87	97	90	
Washington, Ala.	81	94	87	St. Charles, La.	55	137	72	

M = Male Rate

F = Female Rate

OA = Overall Rate

[a] Refers to county shown in "selected cancers" column.

to the general relationship between the relative rates of all cancers and selected cancers. Because this county has a very low population (10,184) and the six counties surrounding it have average populations of only 46,000, a few deaths can reflect in high relative rates. For example, only four cases of esophagus cancer in women in Washington County reflected in a relative rate of 460 for this type of cancer. This indicates that rates for esophagus cancer for women in Washington County, Alabama, are 4.6 times as high as the average rate females in all contagious counties. In such situations relative rates are probably of limited significance, and in any situation they are useful only in conjunction with other data, such as absolute rates.

Table 3-2 shows the absolute rates of all cancers and selected cancers in the 13 counties investigated. The counties are shown in decreasing order of cancer incidence in women. Comments are coded to show counties with high relative rates and elevated absolute rates. Warren County, New Jersey; Salem County, New Jersey; and Erie County, New York, are of particular interest in that they show 10 percent or more elevations in the rates of all cancers rates and selected cancers either in men or women. Rates in these counties are above average in all categories; and rates of selected cancers in males are 23 percent above the national averages in Salem County, New Jersey, and 27 percent above the national average in Erie County, New York. Erie County, New York, also is 18 percent above the national average for all cancers in females. That all three counties have high relative rates suggests that the elevated rates are not attributable to local factors.

Table 3-2. ABSOLUTE RATES OF ALL CANCERS AND SELECTED CANCERS IN THIRTEEN COUNTIES

County/state	All cancers (female)	All cancers (male)	Selected cancers (female)	Selected cancers (male)	Cancer profile comments
Warren, N.J.	147.640^{++}	189.201^{+}	28.242^{+++}	46.198^{+}	(1) (2) (3^{++}) (4^{+++})
Salem, N.J.	146.595^{++}	185.827^{+}	27.133^{++}	54.221^{+++}	(1) (2) (3^{++}) (4^{+++})
Vigo, Ind.	144.191^{++}	180.760^{+}	25.953^{+}	42.105	(1) (2) (3^{++}) (4)
Erie, N.Y.	142.230^{+}	206.966^{+++}	27.454^{++}	56.169^{+++}	(1) (2) (3^{+++}) (4^{+++})
St. Clair, Ill.	138.690^{+}	195.918^{++}	24.060	45.350^{+}	(1) (3^{++})
Summit, Ohio	137.901^{+}	185.488^{+}	25.400^{+}	47.927^{+}	(3^{+}) (4^{+})
Somerset, N.J.	135.655^{+}	182.711^{+}	25.796^{+}	50.384^{++}	(3^{+}) (4^{++})
St. Louis, Mo.	131.979^{+}	181.411^{+}	22.881	42.786	(3^{+})
Kanahwa, W. Va.	126.141	172.278	25.974^{+}	43.605	(1) (2)
Harris, Tex.	124.176	188.483^{+}	22.069	44.348	(1) (2) (3)
Washington, Ala.	114.009	150.645	23.420	36.050	(2)
Brazoria, Tex.	113.951	165.026	21.957	42.923	
St. Charles, La.	112.541	185.710^{+}	27.047^{++}	32.900	(3) (4^{++})

National average: All cancers - 129.974 - female
172.733 - male

Selected cancers - 24.232 - female
44.405 - male

$^{+}$ Above average.
$^{++}$ >10% above average rate.
$^{+++}$ >15% above average rate.

After relative and absolute rates were compared, data on "relative risk" were examined. Relative risk is the ratio of observed cancers to the number that can be anticipated based on overall U.S. rates. Any rate over 100 is considered higher than average. Rates believed to represent "statistically significant" elevations are indicated by National Cancer Institute data. Table 3-3 presents relative risk data. Four counties show significantly high rates for all cancers in both men and women -- Erie County, New York; and Warren County, New Jersey (which showed high relative and absolute rates); St. Clair County, Illinois; and Summit County, Ohio.

Because bladder cancer is the only cancer that is to occur in humans as a result of exposure to amine chemicals, special comparisons are made of bladder cancer rates. Table 3-4 presents relative risk data on bladder cancer. This table also presents "adjusted relative risk" indices. These are relative risk figures on bladder cancer divided by corresponding relative risk figures on all cancers. Adjusted relative risk values over 1.0 indicate that bladder cancer rates are higher than overall cancer rates and suggest that the high rates observed do not result from conditions that cause general high incidences of cancer. Five counties show high bladder cancer rates and adjusted relative risk values greater than 1.0 for both men and women: Salem County, New Jersey; Erie County, New York; Warren County, New Jersey; Summit County, Ohio; and Somerset County, New Jersey. The accumulated values under cancer profile comment also seem to indicate that three counties (Erie, Salem, and Warren Counties in New Jersey) have cancer rate profiles that tend to set them apart from the other counties. Somerset County, New Jersey; and St. Louis County,

Table 3-3. THIRTEEN-COUNTY RANKING BASED ON RELATIVE RISK OF ALL CANCERS

County/state	Combined average for male, female	Male	Female	Cancer profile comments
Erie, N..	115.1	120.3[a]	109.4[a]	(1) (2) (3^{++}) (4^{+++}) (5^{++})
Warren, N.J.	111.5	109.6[a]	113.8[a]	(1) (2) (3^{++}) (4^{+++}) (5^{++})
St. Clair, Ill.	110.5	114.1[a]	106.5[a]	(1) (3^{++}) (5^{++})
Salem, N.J.	109.9	107.9	112.4[a]	(1) (2) (3^{++}) (4^{+++}) (5^{+})
Vigo, Ind.	106.7	103.9	109.8[a]	(1) (2) (3^{++}) (4) (5^{+})
Summit, Ohio	106.3	106.6[a]	106.0[a]	(3^{+}) (4^{+}) (5^{++})
Somerset, N.J.	104.6	105.2	103.8	(3^{+}) (4^{++}) (5)
St. Louis, Mo.	102.7	104.0[a]	101.4	(3^{+}) (5^{+})
Harris, Tex.	102.8	109.7	95.5	(1) (2) (3) (5)
Kanahwa, W. Va.	99.4	101.0	97.6	(1) (2)
St. Charles, La.	94.3	101.5	85.7	(3) (4^{++})
Brazoria, Tex.	92.8	96.0	88.9	
Washington, Ala.	86.8	86.1	87.7	(2)

[a]Statistically significant high relative risk, all cancers.

Table 3-4. THIRTEEN-COUNTY RANKING BASED ON RELATIVE RISK AND ADJUSTED RELATIVE RISK OF BLADDER CANCER

County/state	Relative risk male/female	Adjusted relative risk male/female	Cancer profile comments
Salem, N.J.	245.8*/155.0	2.28/1.38	(1) (2) (3^{++}) (4^{+++}) (5^{+}) (6^{+})
Erie, N.Y.	147.8*/124.7*	1.23/1.14	(1) (2) (3^{+++}) (4^{+++}) (5^{++}) (6^{++})
Warren, N.J.	118.1/141.8	1.08/1.25	(1) (2) (3^{++}) (4^{++}) (5^{++}) (6)
Summit, Ohio	118.1*/117.1	1.11/1.10	(3^{+}) (4^{+}) (5^{++}) (6^{+})
Somerset, N.J.	113.4/128.5	1.08/1.24	(3^{+}) (4^{++}) (5) (6)
St. Louis, Mo.	112.9/106.6	1.09/1.05	(3^{+}) (5^{+}) (6)
Vigo, Ind.	103.5/120.3	<1/1.10	(1) (2) (3^{++}) (4) (5^{+})
St. Charles, La.	113.4/96.8	1.12/1.13	(3) (4)
Harris, Tex.	106.9/96.1	<1/1.01	(1) (2) (3) (5)
St. Clair, Ill.	93.9/102.8	<1/<1	(1) (3^{++}) (5^{++})
Kanahwa, W. Va.	90.9/96.6	<1/<1	(1) (2)
Washington, Ala.	86.9/48.5	1.01/<1	(2)
Brazoria, Tex.	56.8/95.6	<1/1.08	

Missouri (which show high-bladder cancer); and Vigo County, Indiana, constitute a second level in which cancer rate elevations are lower than those of the top three, but higher than those of the remaining eight. It should be noted also that Vigo County had high relative risk of bladder cancer in both men and women, but because the adjusted relative risk for men is slightly under 1.0, it is not coded with a (6).

Table 3-5 shows the 13 counties in order of decreasing evidence of elevated cancer rates. This table also shows population density, degree of industrialization, and the population figures for these counties compared with counties that surround them.

Some of the high relative rates appear to be at least partially explainable from population data. For example, Erie County, New York; St. Louis County, Missouri; Kanahwa County, West Virginia; and Vigo County, Indiana, all have relatively high populations compared with those of surrounding counties. Three of the four show elevated relative cancer rates, as might be expected. Of six counties in which the population is one-tenth or less of the total population of the surrounding counties, four show low relative rates, as might be expected. There is no strong correlation, however, and numerous anomalies are apparent, e.g., Erie County, New York, which has by far the highest general incidence of cancer of any of the counties studied, has a population distribution similar to that of St. Louis County, Missouri, which has comparatively low rates.

Statistics on population density and degree of industrialization are inconclusive because some counties, such as Erie County, New York, and Summit County, Ohio, which have relatively high populations and industrialization factors, have the expected higher cancer rates, whereas such counties

Table 3-5. THIRTEEN-COUNTY POPULATION AND INDUSTRIALIZATION DATA

County/state	Comment	Population density	Industrialization	County population data, 10^3 people	
				Selected county	Contiguous counties total/range
Erie, N.Y.	(1) (2) (3^{+++}) (4^{+++}) (5^{++}) (6^{++})	1006	65(342)	955	546/32-217
Salem, N.J.	(1) (2) (3^{++}) (4^{+++}) (5^{+}) (6^{+})	161	3(23)	48	962/91-488
Warren, N.J.	(1) (2) (3^{++}) (4^{++}) (5^{++}) (6)	175	8(63)	63	888/10-282
Summit, Ohio	(3^{+}) (4^{+}) (5^{++}) (6^{+})	1251	21(257)	454	1927/44-1346
Somerset, N.J.	(3^{+}) (4^{++}) (5) (6)	469	14(85)	139	1390/54-433
Vigo, Ind.	(1) (2) (3^{+}+) (4) (5^{+})	261	5(51)	104	117/15-24
St. Clair, Ill.	(1) (3^{++}) (5^{++})	390	12(92)	204	942/14-652
St. Louis, Mo.	(3^{+}) (5^{+}) (6)	1409	22(224)	652	592/16-207
Harris, Tex.	(1) (2) (3) (5)	722	98(675)	99	273/6-110
St. Charles, La.	(3) (4)	74	4(4)	15	236/9-179
Kanahwa, W. Va.	(1) (2)	279	11(57)	229	272/12-71
Washington, Ala.	(2)	14	2(8)	10	275/7-197
Brazoria, Tex.		54	9(19)	66	1179/20-987

as St. Louis County, Missouri, and Harris County, Texas, which have comparable population densities and degrees of industrialization, have comparatively low rates for cancer frequency. Salem County, New Jersey, is perhaps the most noteworthy exception to the expected. Its relative rates are quite elevated despite the fact that it is smaller than any surrounding county. In addition, its population density and degree of industrialization are low, but it has a high frequency of all cancer categories investigated.

Studies of the correlation between frequency of cancer and the presence of plants producing secondary or tertiary amines, nitric acid plants, plants using amines for production of organic dyes and pigments, or types of chemical facilities in the counties studied were very inconclusive. Results did show that Erie County, New York (the only county with all three kinds of facilities identified as potential contributors to formation of nitrosamines), has the highest rate of cancer that might be anticipated (according to experiments involving nitrosamine exposure of animals). Other counties, however, show inconsistencies from the standpoint of facilities present. For example, St. Charles County, Louisiana, produces both secondary and tertiary amines and has operating nitric acid plants, but it shows little evidence of the occurence of amine-related cancers. Hence, the results observed in Erie County may be purely coincidental.

To put the cancer rates of the 13 selected counties in better perspective, Table 3-6 presents a comparison of the five counties with the highest cancer rates with the six areas in the United States with the highest cancer rates. The rates of the highest areas (in the United States for all cancers and selected cancers) are significantly higher

TABLE 3-6. COMPARISON OF FIVE SELECTED COUNTIES WITH SEVEN COUNTIES WITH HIGHEST NATIONAL RATES OF CANCER

Cancer deaths per 100,000 for 20 yr. period		All cancer		Selected cancers		Bladder cancer		Population density, people/mi^2	Degree of industrialization
		Rate	Rel. Risk	Rel. risk	Adj. rel. risk	Rel. risk	Adj. Rel. risk		
A-in study									
1. Warren	NJ	195.2	111.6	109.5	0.98	125.4	1.12	1,006	65 (542)
2. Vigo	IN	191.8	106.7	99.4	0.93	108.9	1.02	175	8 (63)
3. Erie	NY	181.0	114.9	122.1	1.06	140.7	1.22	161	3 (23)
4. St. Clair	IL	163.9	110.0	101.7	0.92	96.7	0.87	1,251	51 (257)
5. Salem	NJ	163.6	110.6	118.5	1.08	219.0	1.99	469	14 (85)
B-high national									
1. San Francisco	CA	250.5	119.2	124.3	1.04	124.9	1.05	16,309	21 (503)
2. City, St. Louis	MO	242.5	119.5	116.3	0.97	142.8	1.19	12,255	90 (825)
3. Philadelphia	PA	226.3	124.2	122.9	0.99	136.6	1.10	15,584	120 (1812)
4. Baltimore City	MD	224.0	128.3	118.7	0.92	148.1	1.15	12,520	79 (635)
5. N.Y City	NY	223.5	124.1	134.4	1.08	127.9	1.03	25,940	85 (5663)
6. Suffolk	MA	223.1	122.7	123.8	1.01	106.1	0.86	14,207	30 (778)
7. Dist/Columbia	DC	221.4	113.1	106.0	0.94	136.5	1.21	12,442	2 (167)

than those of the five highest study counties. For bladder cancer, however, the five study counties had higher average rates. While this higher average bladder cancer rate is in large part attributable to the very high rate for Salem County, New Jersey, the rates for the other four counties are generally comparable to those observed in the six locations (out of thousands in the U.S. for which data are available) that have the highest overall frequency of occurence of cancer.

TABLE 3-6A. KEY FOR CANCER PROFILE COMMENTS, TABLES 1 THROUGH 6

(1)	Above average relative rate, all cancers.
(2)	Above average relative rate, selected cancers.
(3)	Above average absolute rate, all cancers, male or female.
(3^{+})	Above average absolute rate, all cancers, male and female.
(3^{++})	More than 10% over absolute rate for all cancers, male, female, or both.
(3^{+++})	More than 15% over absolute rate for all cancers, male, female, or both.
(4)	Above average absolute rate, selected cancers, male or female.
(4^{+})	Above average absolute rate, selected cancers, male, and female.
(4^{++})	More than 10% over absolute rate, selected cancers, male, female, or both.
(4^{+++})	More than 15% over absolute rate, selected cancers, male, female, or both.
(5)	Higher than average relative risk, all cancers.
(5^{+})	Significantly high relative risk, all cancers, male or female.
(5^{++})	Significantly high relative risk, all cancers, male and female.
(6)	Higher than average relative risk for bladder cancer, and adjusted relative risk >1.0, male and female.
(6^{+})	Significantly high relative risk for bladder cancer, male or female.
(6^{++})	Significantly high relative risk for bladder cancer, male and female.

4.0 CONCLUSIONS

The search for data on intensity of exposure confirmed that such information is not available from the open literature. Although published data are available on national production of some large-volume chemicals, site-specific data on such things as production rates, process losses, and process discharges are almost completely lacking. Until better sources of information are available, studies such as this one will have to be supplemented with considerable field investigation to identify specific operations that are suitable for in-depth study. It is doubtful whether data collection authority available to health officials under such legislation as the Clean Air Act and Amendments and the Toxic Substances Control Act is adequate to support the activities needed to document human and environmental impacts associated with the production and use of synthetic organic chemicals. The specificity of the current legislated authority, problems of confidentiality, and other related problems present obstacles that would appear to make systematic development of exposure data difficult. Until some way is established to develop such information so that it can be used with existing health data for identification of potential hazards, "kepone" and "vinyl chloride" incidents will continue to be dealt with after considerable damage has already been done. The data analysis techniques presented here can, however, be useful in identifying process discharges that must be studied in detail for definition of their potential environmental impact. Some spe-

cific questions seem to require further county specific investigations. These include:

(1) What factors make Salem County, New Jersey, and Warren County, New Jersey, high in relative rates of cancer, "all cancer" rates, relative risk of selected cancers, and relative risk of bladder cancer despite their low population, population density, and degree of industrialization?

(2) Why is Erie County, New York, highest in cancer rates for all categories studied? Is there a connection between these rates and the known presence of facilities producing and using amines or producing nitrosamine precursors?

(3) What factors make the cancer rates of Summit County, Ohio, high for all cancers, selected cancers, and bladder cancer? (This county was included in the study only because amines are known to be used in rubber processing. No production of amines or nitrosamines has been identified.)

Although other questions are suggested by the assembled data, the absence of evidence to substantiate the exposure of humans to amines or nitrosamines as a result of the investigated industrial activities makes further discussion inappropriate.

As indicated earlier it is felt that the results have confirmed the usefulness of health effects studies and cancer rate data in analysis of potential health impacts associated with the production and use of chemicals. Also the results tend to support certain conclusions as to how such studies should be designed. It appears from the results for bladder cancer studies that it is important to identify a form of cancer that is strongly associated with the chemical(s) being investigated and that the chemical be fairly specific to that form of cancer. The results of the study of selected cancers are similarly interesting from the

standpoint of the lack of association with high rates attributed to smoking. It was known however that nitrosamines are "highly versatile", i.e., apparently capable of producing cancer in animals via any route of exposure and in any organ. It is not surprising therefore that selected cancer rates tended to follow all cancer rates and are apparently relatable to general overall cancer rates. This could be attributable to a) a lack of real association of these cancers with nitrosamine exposure, b) because nitrosamines are so pervasive in the environment and versatile their impact cannot be distinguised from general contamination that is producing high cancer rates, etc. Whatever the reason the results demonstrate the importance of selection of cancer forms for studies of the type reported here.

5.0 RECOMMENDATIONS

Investigations of possible causes of high bladder cancer rates should be undertaken in Salem County, New Jersey; Warren and Somerset Counties in New Jersey; Erie County, New York; and Summit County, Ohio. The potential of the general population exposure to amines, nitrosamines, or other potentially carcinogenic discharges (e.g., coke oven emissions) should be defined. Such investigations should consider all the industries in the counties named and the discharges from them. Discharges should be tested from facilities that appear the most likely to be causing human exposure to a potential carcinogenic and the air and water quality in the vicinity of these facilities should be monitored.

Health records of localities where potentially carcinogenic discharges are believed to be occurring should be studied further (e.g., death certificate information on cases involving bladder cancer should be reviewed to determine whether occupational exposures to amines or nitrosamines might be involved).

The data collection capabilities of the EPA should be examined to see if they are adequate for collection of data to assess the general population exposure to industrial discharges.

Industrial activity and community health should be studied further to evaluate the methodology that has been developed. A study of the possible association between plants producing organic dyes and pigments and the high incidence of bladder cancer might be appropriate.

6.0 HEALTH EFFECTS ASSESSMENT OF AROMATIC AMINES

The activities and types of cancer to be assessed were identified from health effects studies of aromatic amines and nitrosamines. Aromatic amines, which have been linked with bladder cancer in humans, are discussed in this section; nitrosamines, which have been shown to be potent carcinogens in laboratory animal studies, are discussed in Section 7.

Aromatic amines are a particularly potent group of chemical carcinogens. That certain aromatic amines are carcinogenic was first discovered as a result of industrial exposure. In 1895, Rehn reported an ususually high incidence of bladder cancer in workers who had been exposed to a variety of aniline derivatives in the manufacture of dyestuffs.[1] Later β-Naphthylamine, 4-aminodiphenyl, 4-nitrodiphenyl, and 4,4-diaminodiphenyl (benzidine) were implicated in the causation of these so-called aniline cancers.[2]

Epidemiological evidence stimulated interest and subsequently prompted several investigators to attempt experimental induction of bladder cancer in animals to confirm the epidemiological conclusion and to investigate possible biochemical mechanisms of action. In 1938, Hueper and coworkers successfully induced bladder cancer in dogs by subcutaneous injection and chronic oral administration of β-napthylamine.[3] Bonser confirmed these findings in 1943.[4,5] The carcinogenicity of β-Naphthylamine has been demonstrated in several other species, such as the rhesus monkey, mouse,

and hamster (but curiously, not in the rat). Walpole et al. and Deichmann et al. produced carcinomas in dog bladders by oral administration of 4-aminodiphenyl.[9,10] This compound has also been shown to be carcinogenic in man and in several other laboratory animals.[11,12,13]

Benzidine is comparable to β-naphthylamine in carcinogenic potency. Epidemiological and experimental evidence has clearly demonstrated that benzidine is carcinogenic under a variety of conditions.[11,12,13,14] Some aromatic nitro-compounds may be quantitatively converted to aromatic amines or carcinogenic metabolites in vivo.[11] For example, 4-nitrodiphenyl can be reduced fairly readily to the hydroxylamino derivative and thence to 4-aminodiphenyl. Although there are no data on the carcinogenicity of 4-nitrodiphenyl in man, it has induced carcinomas of the bladder when administered orally to dogs.[16]

The list of carefully investigated aromatic amines has been growing since 1950. As far as is known, only aurmine and N, N-bis(2-chloroethyl)2-naphthylamine, along with the compounds listed in the previous paragraph, have demonstrated carcinogenicity in humans. Experimental evidence produced by animal tests suggests that a number of other aromatic amines may have carcinogenic or neoplastic action, as delineated by the list of environmentally hazardous industrial amine chemicals in Section 2.

The urinary bladder is the principal organ affected in man by aromatic amines. Administration of aromatic amines to various species of laboratory animals has caused cancer of the bladder and liver and has provided evidence of cancer induction in many other sites as well. The potency of an administered carcinogenic amine and the sites at which it

will produce cancer are dependent upon the biochemical pathway by which it is metabolized *in vivo*.

In any toxicologic assessment of an environmental contaminant, the way in which humans are exposed to the chemical agent is an important consideration. Possible routes of absorption of aromatic amines into the human body are by inhalation, skin absorption, and ingestion. Industrially, the most common route of entry is penetration through the intact skin. Inhalation is also a common route in occupational settings where there is fine dust or vapor. Inhalation is the principal route of absorption in the general population.

6.1 ACUTE TOXICITY AND NONCARCINOGENIC FORMS OF CHRONIC TOXICITY

Methemoglobinemia is considered the predominant acute reaction to most aromatic amines.[2,16,17] In cases of chemical methemoglobinemia, it is not clear whether the chemical compound implicated has a direct pharmacologic influence on biological systems or the toxic manifestations occur indirectly as a result of hypoxemia. Thus far experimental evidence has been inconclusive, but it is suspected that chemically active aromatic amines directly affect organs.

In the normal function of hemoglobin the iron atom does not undergo a change in valence as oxygen is bound and lost, i.e., it remains as Fe^{+2}. In methemoglobinemia, the iron atom of the heme moiety becomes oxidized from the normal Fe^{+2} (ferrous) state to the abnormal ferric (Fe^{+3}) state. Oxygen bound to methemoglobin is very firmly attached and therefore cannot be used by tissues. Thus, methemoglobin does not function as an oxygen-carrying pigment.

A low concentration of methemoglobin is normally present in blood and maintained by a homeostatic mechanism. Under acute chemical exposure, however, this biochemical mechanism cannot effectively control the amount of abnormal oxidized pigment being produced and clinical cyanosis becomes evident. The onset of cyanosis is usually insidious. It depends on the rate of absorption and the specific agent absorbed. Often the first sign of cyanosis is a violet color in the lips and ears. The color is usually more intense than that produced by cyanosis associated with unoxygenated normal hemoglobin. Symptoms of intoxication include euphoria, flushed appearance, and headache, and may extend to muscular weakness, ataxia, light-headedness, dyspnea, tachycardia, and alarming cyanosis. If absorption continues, coma, cardiac failure, and even death may result. Cyanosis is usually detectable when the methemoglobin concentration in the blood reaches 15 percent, but definitive symptoms may not occur at levels as high as 40 percent. The effects of methemoglobinemia are reversible, and recovery is usually complete if exposure to the oxidizing agent is terminated soon enough.

Discussion of the biochemical mechanism(s) by which methemoglobin is formed as a result of exposure to aromatic amines is not within the scope of this toxicologic assessment. It should be noted, however, that metabolites (e.g., phenylhydroxyl amines and nitroso derivatives) rather than the aromatic amines themselves are believed to be the proximate cause of blood pigment oxidation.[2,18] Similarly, metabolic derivatives of aromatic amines have been implicated in the mechanisms of chemical carcinogenesis. The methemoglobin-producing capabilities of aromatic amines appear to be directly related to their carcinogenic potential.[19]

This observation may eventually prove to be chemically significant.

Secondary or accompanying effects of induced methemoglobinemia (other than the formation of methemoglobin, which are not well characterized) may obscure other possible acute manifestations reflecting direct toxicity. Reportedly, hemolysis is frequently associated with the absorption of methemoglobin-forming compounds, but not all investigators would agree unequivocally. Hamblin and coworkers, for example, observed numerous cases of methemoglobinemia, but were unable to find clinical evidence of increased hemolysis.[18] Scott, on the other hand, reports that a secondary anemia may result from the consequent hemolysis after prolonged or intensive exposure to aromatic amines.[16]

Many reports have mentioned the appearance of Heinz bodies (small refractile granules in the erythrocytes) following exposure to aromatic amines.[16,18] It is evident from the early literature that the significance of Heinz bodies in red blood cells was not fully understood or agreed upon. More recent reviews of aromatic amine toxicity rarely ever mention Heinz bodies. In any case, their recognition seems to be of little practical clinical significance. Similarly, references to changes in bone marrow, inflamation of the respiratory tract, and involvement of the gastrointestinal and neurological systems are also found in the early literature; however, such effects are not documented, characterized, or substantiated well enough to be regarded as toxic manifestations of aromatic amine intoxication.

Current evidence indicates that liver damage is not a common hazard associated with chronic aromatic amine exposure. In the case of some aromatic amines, however, the liver may be involved when severe exposure raises the level

of absorption high enough to induce acute intoxication, although none of the literature describes specifically how the liver is affected. Liver damage as well as hepatic tumors (benign or malignant) has been induced in many different animal models by numerous aromatic amines, but dosages usually have been large and have continued over prolonged periods.

According to Scott, chemical cystitis is well recognized as an acute effect of some aromatic amines.[16] This condition, which can be induced by some toluidines and chlorotoluidines, has been observed in individuals following occupational exposure. Cystitis may be accompanied by painful and frequent micturition and hematuria symptoms often mistaken as those of bladder cancer.

The only other evidence of toxicity of aromatic amines is irritation of the cornea, lung tissues, and mucous membranes. Such minor effects may be properly attributable to specific compounds, but they occur only after chronic or subchronic intoxication.[14] Thus, methemoglobinemia can be considered the outstanding acute effect of aromatic amine exposure. The most serious effect of chronic toxicity of industrial aromatic amines is, of course, that of carcinogenicity.

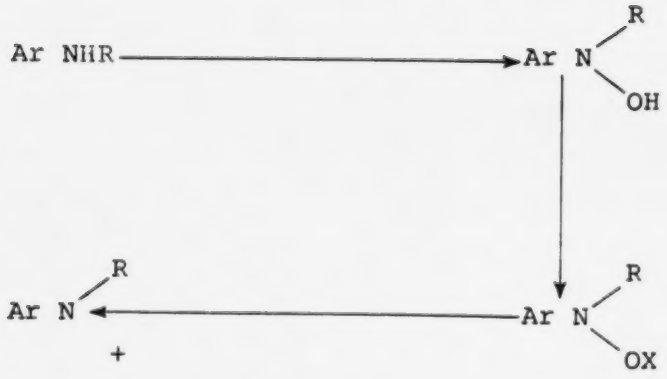
6.2 CARCINOGENICITY

Certain aromatic amines were first discovered to be carcinogenic in man as a result of industrial exposure. The carcinogenic manifestation usually appears in the urinary bladder following a latent period of 15 to 20 years.[20] Toxicologic studies on the induction of bladder cancers by aromatic amines in laboratory animals show how differences in metabolic pathways may affect carcinogenicity. The accumulating experimental evidence supports the view that

aromatic amines themselves are not carcinogenic, but they give rise to carcinogenic metabolites in vivo. For example, β-naphthylamine is biotransformed by the liver to β-naphthylhydroxylamine (the N-hydroxyl derivative) and other metabolites. When β-naphthylamine itself was implanted directly in the bladder of mice, it did not induce tumors. On the other hand, the hydroxylamine derivative proved to be a potent carcinogen in this system.[21,22]

Present evidence indicates that metabolic activation is required before aromatic amines can elicit carcinogenic action.[5] N-hydroxylation is the important biochemical mechanism by which an aromatic amine is converted to its active carcinogenic intermediate. Esterification of the hydroxyl groups occurs in some, but probably not all, activation processes. The final N-hydroxylation product is unstable and dissociates to an electrophile, which can interact with tissues and ultimately induce biochemical changes. Figure 6-1 is a simplified schematic representation of the metabolic activation of aromatic amines.

The oxidation of primary and secondary amines is the major route by which N-hydroxy compounds are formed. This enzymatic oxidation occurs primarily in the liver by a mixed function oxidase dependent reaction, but it can take place in several other organs as well. These tissues may have some other activating enzymes, such as transacetylase or peroxidase, that can produce a reactive ester form. Although N-hydroxylation is necessary for tumor induction by carcinogenic aromatic amines, it should be noted that all N-hydroxy derivatives are not carcinogenic. In addition, some aromatic amines cannot be enzymatically N-hydroxylated and therefore are not carcinogenic.



Ar = aryl
R = H, acyl, or alkyl
X = ester group

FIGURE 6-1. Scheme for metabolic activation of aromatic amines.[5]

Once the N-hydroxy compound is formed, it is subjected to competing metabolic pathways. The carcinogenic metabolites of aromatic amines may be rapidly conjugated with glucuronic acid in the liver. This detoxification mechanism usually protects the tissues from exposure to the carcinogens because the glucuronides are not biologically active and are excreted in the urine. Under the appropriate pH conditions, the action of β-glucuronidase, an enzyme present in the urine of some species, can hydrolyze glucuronides and release free carcinogens in the ureters and bladder, which ultimately leads to the formation of malignant lesions at these sites. Humans and dogs apparently have the necessary biochemical mechanism for transforming these aromatic amines into active carcinogens.[23] Experimental evidence has demonstrated that the carcinogenic activity responsible for producing bladder cancer is present in the urine rather than in the bladder circulation.

Oral administration of β-glucuronidase inhibitor (glucosaccharo-1,4-lactone) simultaneously with β-naphthylamine greatly reduces the incidence of bladder tumors in dogs.[20] Similar treatment with β-glucuronidase inhibitors has been proposed as a prophylactic measure for people who are accidentally exposed to carcinogens of this type. Unusually high urinary levels of β-glucuronidase have been observed in patients with bladder tumors induced by chronic exposure to naphthylamine. It is not yet clear whether these elevated enzyme levels preceded the development of the neoplasms, but if so, this may be indicative of how an individual may be genetically predisposed to a particular kind of cancer.

The target site of a carcinogenic aromatic amine is influenced by its metabolic pathway, the specific structure

of the aryl moiety, the route of administration, and the species to which the compound is administered. The urinary bladder is the organ most commonly affected in humans who are occupationally exposed to certain of the aromatic amines. For example, β-naphthylamine is a known potent bladder carcinogen in humans. Similarly, oral administration of this compound induces bladder tumors in dogs, monkeys, and hamsters. The compound induces liver tumors in mice, but rats and rabbits are resistant to carcinogenesis at any site.[5] Subcutaneous injection of benzidine induces liver tumors, ear duct carcinomas, and adenocarcinomas of the intestine in rats, whereas it induces only hepatomas in mice.[5] When fed to rats, 2-acetylaminofluorine, 4-aminodiphenyl, and 4-aminostilbene cause cancers at many sites in the body, but especially in the sebaceous gland of the external ear duct and in the intestine, liver, and kidney.[20] Other examples of experimental induction of malignant neoplasms by aromatic amines at various organ sites are too numerous to mention here. It should be evident from the examples cited, however, that several endogenous and exogenous factors can affect the potency of a carcinogenic aromatic amines and the sites at which they can induce cancer, Table 6-1 summarizes the carcinogenic effects of some specific compounds that are included in the list of environmentally hazardous industrial amine chemicals covered by this study.

Several important structure-activity relationships useful in predicting the carcinogenicity of aromatic amines have already been mentioned. There is strong experimental evidence that N-hydroxylation is the primary stage in conversion of aromatic amines to their ultimate carcinogenic form. In certain compounds a further activation step may be

Table 6-1. CARCINOGENICITY OF SOME AROMATIC AMINES [5]

Compound	Species	Route[a]	Adequacy[b]	Site of tumor induction[c]							
				Local	Bladder	Kidney	Liver	Intestine	Ear Duct	Breast	Other
Auramine	Rat	S.C./O	S	-	-	-	+	-	-	-	-
	Mouse	O	S	-	-	-	+	-	-	-	-
Benzidine	Dog	O	A	-	?+	-	-	-	-	-	-
	Hamster	O	S	-	-	-	+	-	-	-	-
	Rat	S.C.	A	-	-	-	+	+	+	-	-
	Mouse	S.C.	S	-	-	-	+	-	-	-	-
β-Naphthylamine	Mouse	O	A	-	-	-	+	-	-	-	-
	Rat	O	A	-	-	-	-	-	-	-	-
	Hamster	O	S	-	+	-	-	-	-	-	-
	Rabbit	O	S	-	-	-	-	-	-	-	-
	Cat	O	S	-	-	-	-	-	-	-	-
	Dog	O/S.C.	A	-	+	-	-	-	-	-	-
	Monkey	O	S	-	+	-	-	-	-	-	-
4-Aminobiphenyl	Mouse	O	S	-	?	-	+	-	-	-	-
	Rat	O	A	-	-	-	?	?	-	+	-
	Hamster	O		-	-	-	-	-	-	-	-
	Rabbit	O	S	-	+	-	-	-	-	-	-
	Dog	O	A	-	+	-	-	-	-	-	-
N,N-Bis(2-chloroethyl)-2-naphthylamine	Mouse	I.P.	S	-	-	-	-	-	-	-	+
4,4'-Methylenedianiline	Rat	O/S.C.	A	-	-	-	?	-	-	-	-
3,3'-Dichlorabenzidine	Rat	O/S.C.	A	-	+	-	-	+	+	+	Skin, lymphoma
	Hamster	O	S	-	+	-	+	-	-	-	Bone
4,4'-Methylene bis(2-chloroaniline)	Rat	O/S.C.	A	-	-	-	+	-	-	-	Lung
	Mouse	O	S	-	-	-	+	-	-	-	Hemangio-sarcoma
O-Tolidine	Rat	S.C.	A	+	-	-	-	-	+	+	Lymphoma, skin
O-Dianisidine	Hamster	O	S	-	?	-	-	-	-	-	Fore-stomach
	Rat	O	S	-	-	-	-	-	?	-	-

[a] O, oral; S.C., subcutaneous injection; I.P., intraperitoneal injection.

[b] A, tested in more than one institute; S, evidence less convincing.

[c] +, tumors reported; -, tumors not reported; ?, evidence equivocal.

necessary. The effect of different aromatic structures, alkyl or aryl groups, or different esters on the biosynthetic and dissociation stages are difficult to characterize accurately with currently available data. Nevertheless, a few generalizations regarding the structure of aromatic amines and their activity can be drawn from the literature.

Potent carcinogenicity is associated with aromatic groups consisting of two or more conjugated or fused aromatic rings. Single aromatic (or nonconjugated) ring systems may be carcinogenic is some cases, but present evidence indicates that much higher doses are required [e.g., O-toluidine, 4,4'-methylene bis(2-chloroaniline), 2, 4,6-trimethylaniline, toluene-2,4-diamine, 5-chlorotoluidine]. Aromatic rings in which the group para to the amino group is substituted are generally more carcinogenic than those in which the para position is unsubstituted.

The aryl or alkyl group on the amino nitrogen can modify the carcinogenicity of a carbocyclic aromatic amine by interfering with N-hydroxylation. The effect of R (in $\begin{matrix} Ar \\ R \end{matrix}$ N+) on carcinogenicity becomes progressively less, activating in the order: OX > OH[NO] > H, $COCH_3$, CH_3, $[NO_2]$ > COA > A > COAr > SO_2Ar (where X = esterifying groups, A = alkyl other than methyl, Ar = aromatic ring, [NO] represents arylnitrosamine, $[NO_2]$ represents nitroarene).[5]

The effect of certain substitutions in the aryl ring on the carcinogenicity of the compound is fairly constant. Substitution of a methyl or methoxy group ortho to the aromatic amino group, for example, often enhances reactivity, whereas sulfonic acid derivatives are often without reactivity.

Aromatic amines are one of the few groups of chemical carcinogens for which there is convincing evidence that some members induce cancer in humans, which is a significant reason why animal studies with those compounds must be considered particularly relevant to man, who demonstrates similar metabolic capabilities. Our present approach to carcinogenesis (i.e, large scale use of animal experimentation) may provide qualitative information, but the important quantitative considerations with regard to chemical carcinogenesis (e.g., dose-response relationships) cannot be accurately assessed without comprehensive epidemiological investigations encompassing both clinical and environmental findings.

A number of short-term tests like the Ames mutagenesis test and other bioassay systems, which rely on the biologic detection of activated metabolites, have begun to be used on a large scale and may prove to be an effective screening method for environmental carcinogens. Correlations between bioassay results and human experience or experimental data cannot be established at this time because of the limited amount of bioassay data.

Noncarcinogenic aromatic amines or other amino compounds can react with nitrites and, under the proper environmental conditions, form carcinogenic nitrosamines. The health effects and environmental significance of this class of chemical carcinogens are discussed in Section 7.

6.3 HISTORICAL EPIDEMIOLOGY OF AROMATIC AMINES

Historically, epidemiological studies focusing on the effects of exposure to aromatic amines have established that, at least occupationally, many aromatic amines are potent human bladder carcinogens. In 1895, Rehn first reported four cases of bladder cancer in a group of 45 men employed in the manufacture of fuchsin.[1] Although aniline

was the first of the amines to come under suspicion, it is fairly certain that the dyestuffs industry workers studied by Rehn must have been exposed to a number of other chemical intermediates. Aniline was eventually exonerated by later studies, and several compounds were singled out as highly suspect aromatic amine bladder carcinogens.[2,24] By 1950 a substantial body of experimental and clinical evidence had been gathered linking occupational bladder cancer with aromatic amine exposure in dyestuffs industry workers. At that time Robert Case and his colleaques began their classic epidemiological studies of the British dyestuffs industry.[25]

Case's project was one of the most exhaustive epidemiological studies ever undertaken. By 1952 he had been able to locate 455 cases of bladder tumors in the British chemical industry and was able to establish that 311 of these occurred in men known to have worked with benzidine, α-naphthylamine, β-naphthylamine, auramine, and magenta. Case calculated that the chance of someone working with β-naphthylamine developing a bladder cancer was 61 times greater than that of the general population; someone working with benzidine, 19 times greater; and someone exposed to commercial α-naphthylamine, 16 times greater. Case also noted that occupation-related cancers occurred at a much earlier age than those not thus related. He established that the latent period for tumor induction averaged 16 years for those who worked with β-naphthylamine and benzidine.

Another study (by Williams) of men drawn from the same population studied by Case gave striking evidence of the effects of severe exposure conditions.[26] He described a group of 78 men engaged in distilling β-naphthylamine and benzidine under poor working conditions. He found 35 men

(54%) had developed bladder tumors, and the incidence increased sharply with longer exposure times. Seven cases (16%) were found among 43 men with less than 3 years of exposure, 11 cases (65%) among 17 men with 3 to 5 years of exposure, and 17 cases (94%) among 18 men with 5 or more years of exposure.

Case made an almost coincidental observation that led him to his most significant finding. While examining regional mortality data, he observed a high prevalence of bladder cancer among a group of men who worked in one large rubber factory. During the years 1936 through 1950, 22 cases were found, whereas only 4 would have been predicted. Simultaneously, inquiries revealed that rubber antioxidants then in use were manufactured from α- and β-naphthylamine and that men involved in the manufacturing of these antioxidants were also suffering from bladder cancer.

Exposure to aromatic amines in the rubber industry has been of a different character from that occurring in the chemical industry. The intensity of the hazard, presumably resulting from small impurities of β-naphthylamine, has been relatively low. In his 1969 study Veys showed that the overall incidence of bladder cancer among rubber industry workers was only four times that of the general population.[27]

Some epidemiological evidence shows that the use of carcinogenic antioxidants presents the greatest risk to rubber industry workers who are involved either in the compound mixing or final vulcanizing, both high-temperature operations.[16] In addition, Scott (1962) indicated the probable extension of the aromatic amine hazard to cable manufacturers (users of identical antioxidants), makers of pigments and paints (users of similar intermediates), the paper industry (users of auramine and magenta), and of

course, numerous scientific and medical laboratories (users of benzidine).[16]

6.4 EPIDEMIOLOGICAL EVIDENCE LINKING INDIVIDUAL AROMATIC AMINES WITH HUMAN CARCINOGENESIS

The general discussion of the epidemiology of aromatic amine cancers in the previous section clearly illustrates the human health hazards posed by these compounds. This section presents epidemiological evidence linking highly suspect or industrially important aromatic amines in individual compounds with human carcinogenesis. The purpose is to provide a summary of the potential environmental health hazards posed by individual aromatic amines. More detailed discussions of the epidemiology of aromatic amine cancers can be found in the following two excellent monographs:

1. International Agency for the Research of Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man.[12,15]

2. American Chemical Society (ACS) Monograph 173, Chemical Carcinogens.[5]

4-Ambinobiphenyl

Melick and coworkers studied a population of 171 male workers exposed to 4-aminobiphenyl between 1935 and 1955, individual exposure times varied from 1.5 to 19 years.[28] Nineteen men (11.1%) had developed bladder tumors. In a follow-up study, Melick examined 315 male workers and found 53 men with bladder tumors; however, the exact exposure times could not be established in this study.[29] Melamed et al. and Koss et al. found 35 histologically proven cases of carcinoma of the bladder in their study population of 503 men exposed to 4-aminobiphenyl.[30,31,32] Figure 6-2 illustrates the results of these studies and the way in which tumors developed in the exposed population.

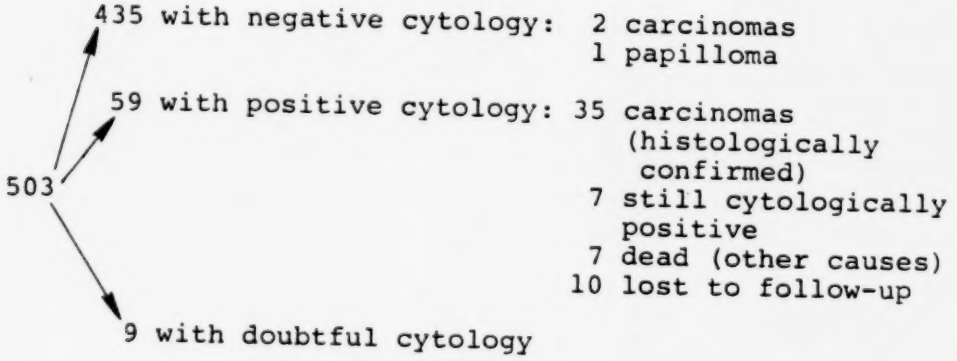


Figure 6-2. Development of bladder tumors among 503 workers, 1960-68.[32]

Auramine

In 1959, a study by Case and Pearson indicated a high incidence of bladder tumors among English workers involved in the manufacture of auramine.[33] Within the study population, six deaths occurred from bladder cancer, whereas only 0.13 would have been expected from the whole male population of England and Wales ($p < 0.005$). The latent period from the start of exposure to detection of the tumors ranged from 9 to 28 years and averaged 19.3 years.

Benzidine

The first study linking benzidine with human bladder cancer in workers was reported before 1940.[34] A high incidence of bladder tumors was observed in workmen exposed to benzidine in British chemical plants; 10 deaths occurred from bladder cancer, whereas only 0.72 would have been expected from the whole male population of England and Wales ($p < 0.001$).[25] In a cohort study of a factory population, it was reported that benzidine had an "attack rate" of 237 per 100,000 persons exposed.[35] A retrospective study of a single plant showed that 17 out of 76 workmen exposed only to benzidine developed bladder tumors.[36] In another study, it was noted that 6 of 19 benzidine-exposed workers autopsied had primary tumors at sites other than the bladder, whereas none of the 14 β-naphthylamine-exposed workers autopsied showed primary tumors at sites other than the bladder.[37] Although the findings of this study are controversial, they are indicative of the possible multiple-organ carcinogenicity of benzidine.

N,N-Bis(2-chlorethyl) 2-naphthylamine (chlornaphazine)

As of 1970, 14 cases of bladder cancer associated with the use of chlornaphazine had been reported in the

literature.[38,39,40] Thiede et al. collected data on 61 polycythemia vera patients treated with chlornaphazine and 40 such patients not treated with this drug.[38] Seven of the patients treated with chlornaphazine developed bladder tumors not associated with either cigarette smoking or occupational factors. None of the patients who had not been treated with chlornaphazine developed bladder tumors. Although it had originally been thought that a dose of more than 100 grams of chlornaphazine was necessary to induce bladder tumors, it was reported that one bladder tumor developed in a patient who had received only 4 grams and one incidence of abnormal urinary cytology occurred in one who had received only 2 grams.[40]

β-Naphthylamine

Case et al. showed that there were 26 certified deaths from cancer of the bladder in workers exposed to β-naphthylamine, whereas only 0.3 would have been expected from the whole male population of England and Wales ($p < 0.001$).[25] In a cohort study of a factory population it was reported that β-naphthylamine had an "attack rate" of 952 per 100,000 exposed population.[35] Goldwater et al., in a study of coal-tar dye plant workers, showed that 12 out of 48 workmen exposed only to β-naphthylamine developed bladder tumors.[36]

Table 6-2 summarizes some of the salient features of the five compounds discussed in the previous section. The five compounds listed are those aromatic amines for which an undeniable amount of epidemiological evidence has indicated human carcinogenic activity. It should be emphasized that these are not the only aromatic amines that may represent a significant carcinogenic hazard to man. Many other aromatic amines are highly carcinogenic in animals, and there is no reason to suspect that man will be immune to their carcinogenic potential.

TABLE 6-2. AROMATIC AMINES FOR WHICH CARCINOGENICITY OR A STRONG SUSPICION OF CARCINOGENICITY TO MAN HAS BEEN FOUND.[41]

Aromatic amine	Type of exposure	Target organ	Route of exposure	Exposure level
4-Aminobiphenyl	Occupational	Bladder	Inhalation, oral	Unknown
Auramine	Occupational	Bladder	Oral, inhalation skin	Unknown
Benzidine	Occupational	Bladder	Oral, inhalation, skin	Unknown
Chlornaphazine	Medical	Bladder	Oral	4-350g (total dose)
β-Naphthylamine	Occupational	Bladder	Inhalation, oral	Unknown

REFERENCES

1. Rehn, L. Blasengeschwülste Bei Fuchsin-arbeitern. Arch. Klin, Chir., 50: 588,1895.

2. Hamilton, A., and H. L. Hardy. Aromatic Nitro and Amino compounds. In: Industrial Toxicology, 3rd edition, Publishing Sciences Groups, Inc., Acton, Mass., 1974. pp. 305-311.

3. Hueper, W. C., J. H. Wiley, and H. D. Wolfe. Experimental Production of Bladder Tumors in Dogs by Administration of Beta-Napthylamine. J. Ind. Hyg. 20: 46-84, 1938. [cited in (5, 12)]

4. Bonser, G. M., and J. Pathol. Bacteriol., 55: 1, 1943. [cited in (5)]

5. Searle, C. E. Chemical Carcinogens, ACS Monograph 173. American Chemical Society, Washington, D.C. 1976.

6. Clayson, D. B. Chemical Carcinogenesis. Little Brown and Co., Boston, 1962. [cited in (9)]

7. Saffiotti, U., J. Cefis, R. Montesano, and A. R. Sellakumar. Induction of Bladder Cancer in Hamsters Fed Aromatic Amines. In: Inter-American Conference on Toxicology and Occupational Medicine. Bladder Cancer; A Symposium. Aesculapius Pub. Co., Birmingham, Alabama, 1967. pp. 129-35. [cited in 9]

8. Conzelman, G. M. and J. E. Maulton. Dose-Response Relationships of the Bladder Tumorigen 2-Naphthylamine: A Study in Beagle Dogs. J. National Cancer Inst., 49: 193-205, 1972. [cited in (9)]

9. Walpole, A. L., M. H. C. Williams, and D. C. Roberts. Tumours of the Urinary Bladder in Dogs After Ingestion of 4-Aminodiphenyl. Brit. J. Ind. Med., 11; 105, 1954. [cited in (12)]

10. Deichmann, W. B., J. L. Radomski, W. A. D. Anderson, M. M. Coplan, and F. M. Woods. The Carcinogenic Action of p-Aminobiphenyl in the Dog, Final Report. Ind. Med. Surg., 27: 25, 1958. [cited in (12)]

11. Weisberger, J. H. Chemical Carcinogenesis. In: Toxicology. The Basic Science of Poisons. L. J. Casarett and J. Doull (eds.). MacMillan Publising Co., Inc., New York, 1975. pp. 333-378.

12. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 1. IARC, Lyon. 1972.

13. Suspected Carcinogens, 2nd edition. A subfile of the Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health, Cincinnati, Ohio. 1976.

14. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values for Substances in Workroom Air, 3rd edition. Cincinnati, Ohio, 1976.

15. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4. IARC, Lyon. 1974.

16. Scott, T. S. Carcinogenic and Chronic Toxic Hazards of Aromatic Amines. Elsevier Publishing Co., New York, 1962.

17. Bodansky, O. Methemoglobin and Methemoglobin-producing Compounds. Pharmac Rev. 3: 144, 1951. [cited in (2)]

18. Hamblin, D. O. Aromatic Nitro and Amino-Compounds. In: Industrial Hygiene and Toxicology, 2nd edition, Vol. II. F. A. Patty (ed.). Interscience Publishers, New York, 1963. pp. 2105-69.

19. Radomski, J. L., and E. Brill. Bladder Cancer Induction by Aromatic Amines: Role of N-Hydroxy Metabolites. Science, 167: 992, 1970. [cited in (5)]

20. Goldstein, A., L. Aronow, and S. M. Kalman. Chemical Carcinogenesis. In: Principles of Drug Action: The Basis of Pharmacology, 2nd edition. John Wiley and Sons, New York, 1974. pp. 667-702.

21. Bonser, G. M., D. B. Clayson, and J. W. Jull. Some Aspects of the Experimental Induction of Tumours of the Bladder. Brit. Med. Bull., 14: 146, 1958. [cited in (20)]

22. Clayson, D. B. The Aromatic Amines. Brit. Med. Bull., 20: 115, 1964. [cited in (20)]

23. Troll, W., and S. Belman. Studies on the Nature of the Proximate Bladder Carcinogens. In: Inter-American Conf. on Toxicology and Occupational Medicine. Bladder Cancer; A Symposium. Birmingham, Alabama. Aesculapius, 1967. [cited in (2)]

24. International Labour Office. Studies and Reports, Series F, No. 1, 1921. p. 6.

25. Case, R. A. M., M. E. Hasker, D. B. McDonald, and J. T. Pearson. Tumors of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. I. The Role of Aniline, Benzidine, alpha-Naphthylamine and beta-Naphthylamine. Brit. J. Ind. Med., 11: 75, 1954.

26. Williams, M. H. C. Occupational Tumors of the Bladder. In: Cancer, Vol. 3, R. W. Raven, ed., Butterworths, London. 1958. p. 337.

27. Veys, C. A. Two Epidemiological Enquiries into the Incidence of Bladder Tumours in Industrial Workers. J. National Cancer Institute, 43: 219, 1969.

28. Melick, W. F., H. M. Escue, J. J. Naryka, R. A. Mezera, and E. R. Wheeler. The First Reported Cases of Human Bladder Tumors due to a New Carcinogen - Xenylamine. J. Urol., 74: 760, 1955.

29. Melick, W. F., J. J. Naryka, and R. E. Kelly. Bladder Cancer due to Exposure to para-Aminobiphenyl: A 17-year Follow-up. J. Urol., 106: 220, 1971.

30. Melamed, M. R., L. G. Koss, A. Ricci, and W. F. Whitmore. Cytohistological Observations on Developing Carcinoma of Urinary Bladder in Man. Cancer, 13: 67, 1960.

31. Koss, L. G., R. Myron, M. R. Melamed, A. Ricci, W. F. Melick, and R. E. Kelly. Carcinogenesis in the Human Urinary Bladder. Observations after Exposure to para-Aminodiphenyl. New Engl. J. Med., 272: 767, 1965.

32. Koss, L. G., R. Myron, M. R. Melamed, and R. E. Kelly. Further Cytologic Studies of Bladder Lesions in Workers Exposed to para-Aminodiphenyl: Progress Report. J. Nat. Cancer Inst., 43: 233, 1969.

33. Case, R. A. M., and J. T. Pearson. Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Part II. Further Consideration of the Role of Aniline and of the Manufacture of Auramine and Magenta (Fuchsine) as Possible Causative Agents. Brit. J. Ind. Med., 11: 213, 1954.

34. Hueper, W. C. Occupational Tumor and Allied Diseases. Thomas Pub., Springfield, Ill., 1942.

35. Mancuso, W. C., and A. A. El-Attar. Cohort Study of Workers Exposed to beta-Naphthylamine and Benzidine. J. Occup. Med., 9: 277, 1967.

36. Goldwater, L. J., A. J. Rosso, and M. Kleinfeld. Bladder Tumors in a Coal Tar Dye Plant. Arch. Environm. Hlth., 11: 814, 1965.

37. Von Ubelin, F., and A. Pletscher. Atiologie and Prophylaxe gewerblicher Tumoren in der Farbstoff-Industrie. Schweiz Med. Wschr., 84: 917, 1954.

38. Thiede, T., E. Chievitz, and B. C. Christensen. Chlornaphazine as a Bladder Carcinogen. Acta Med. Scand., 176: 45, 1964.

39. Laursen, B. Cancer of the Bladder in Patients Treated with Chlornaphazine. Brit. Med. J., 111: 684, 1970.

40. Thiede, T., and B. C. Christensen. Bladder Tumours Induced by Chlornaphazine-treated Patients with Polycythaemia. Acta Med. Scand., 185: 133, 1969.

41. International Agency for Research on Cancer. Annual Report-1975. IARC, Lyon, 1975.

7.0 HEALTH EFFECTS ASSESSMENT OF NITROSAMINES

Research on nitrosamine toxicity and carcinogenesis was initiated after evidence was found of human toxicity arising from industrial exposure to dimethylnitrosamine.[1] The principal toxic effect described in early occupational accounts was that of liver damage. The possible occurrence of nitrosamines in other than industrial environments was not suspected until considerably later (1960), when an outbreak of serious liver disease in sheep was reported in Norway.[2] Postmortem examination revealed severe liver necrosis as the main pathological manifestation. All the affected sheep were found to have been fed a diet containing fish meal preserved with nitrite. Since fish contain relatively large amounts of secondary and tertiary amines, it was suggested that nitrosamines had been formed. Ender et al. identified dimethylnitrosamine as the key toxic constituent in this fish meal and reported concentrations as high as 30 to 100 ppm.[3] Pure dimethylnitrosamine was shown in experience to induce liver lesions in sheep very similar to those observed in animals that had received the toxic fish meal. This clear indication that enough dimethylnitrosamine could be formed to kill the animals obviously raised the possibility that small quantities of this or other nitrosamines might occur in other foods, including those for human consumption, perhaps at concentrations not high enough to cause overt toxic effects but sufficiently high to induce cancer if the consumption of such food were continued for extended periods of time.

Following the discovery by Magee and Barnes of the toxic and carcinogenic actions of dimethylnitrosamine in experimental animals, the biological activities of a variety of N-nitroso compounds were extensively investigated.[5] Work focused principally on their biochemical modes of action and on their carcinogenicity in animals. The results of such research indicated that the N-nitrosamines are among the most potent and versatile of all chemical carcinogenic agents. These compounds have induced cancer in over 20 species tested via all routes of exposure in essentially all vital organs.

The occurrence of N-nitroso compounds in the environment and their formation in the body have also been topics of interest. The synthesis of N-nitroso compounds from secondary amines and nitrosating agents has been well known since 1865, when it was found that dimethylamine hydrochloride treated with sodium nitrite in an aqueous solution at an acid pH formed a high yield of N-nitrosodimethylamine.[6] It was suggested that this reaction could occur under the acid conditions prevailing in the mammalian stomach from ingested nitrites and amines. There is now considerable evidence that nitrosamines can be formed in this way.

Nitroso compounds, and their precursors, are widespread in all media of the environment as the result of contributions of both natural and manmade sources. N-nitrosamines, nitrate, nitrite, and nitrosatable amines may be present in foodstuffs, water supplies, or the air we breathe. Nitrogen oxides and airborne amines can combine easily under certain circumstances to form nitrosamines and other potential carcinogens.[7] Due to the low levels of occurrence of these substances and the absence of dose-response data, however, the consequence of this exposure in terms of human cancer is unknown.

Thus, the possible occurrence of nitrosamines in human and animal food, the realization of their potential for much wider environmental distribution, and the important discovery that nitrosation could occur in vivo when nitrite and suitable substrates are ingested all suggest that this class of compounds may pose a potential threat to public health. This brief health effects assessment will address the various biological actions of nitrosamines, including the production of acute and chronic cellular injury, carcinogenesis, mutagenesis, and teratogenesis.

7.1 ACUTE TOXICITY

For the purpose of discussing the toxicity of N-nitroso compounds, previous reviews have often divided them into two groups; the N-nitrosamines and the N-nitrosamides. Although amides are excluded by the restricted amines definition in this report (primarily for quantitative considerations), the biological action of nitrosamides is considered significant in view of their instability at physiological pH and their probable decomposition to active intermediates analogous to those derived from nitrosamines.

The potency of N-nitroso compounds in causing acute tissue injury and death varies considerably, as shown in Table 7-1. Acute toxicities of N-nitrosamines and N-nitrosamides, expressed as single dose oral LD_{50} values in adult rats, range from a low of 18 mg/kg to more than 5000 mg/kg. Many of these compounds are moderately toxic, having LD_{50}'s between 150 and 500 mg/kg.

The nitrosamines, with some exceptions, are selectively hepatotoxic, while the nitrosamides induce damage predominantly in organs of rapid cell turnover, such as the gastrointestinal tract, the blood-forming organs, and the lymphoid system.[9] The histopathology of acute intoxication

Table 7-1. ACUTE TOXICITY OF SOME N-NITROSO COMPOUNDS[8]

Compound	LD_{50}[a]
Dimethylnitrosamine	27 to 41
Diethylnitrosamine	216
Di-n-propylnitrosamine	>400[b]
Di-n-butylnitrosamine	1200
Di-n-amylnitrosamine	1750
Methyl-n-butylnitrosamine	130
Methyl-t-butylnitrosamine	700
Ethyl-n-butylnitrosamine	380
Ethyl-t-butylnitrosamine	1600
Ethyl-2-hydroxyethylnitrosamine	>7500
Di-2-hydroxyethylnitrosamine	>5000
Methylphenylnitrosamine	200
Methylbenzylnitrosamine	18
Nitrosomorpholine	282
Methylnitrosourea	180
Methylnitrosourethane	240
Nitrosohexamethyleneimine	336
Nitrosoheptamethyleneimine	283
Nitrosooctamethyleneimine	566

[a] LD_{50} units: mg/kg body weight, single oral dose, adult male rats.

[b] Male and female Syrian golden hamsters.

from dialkyl and cyclic nitrosamines is well-documented, and toxic effects have been demonstrated in a wide range of mammalian species. The primary acute effect induced by these compounds is liver damage, characterized by a hemorrhagic type of centrilobular necrosis.[8,9] The liver lesion is commonly accompanied by heavily blood-stained ascites, hemorrhages into the gastrointestinal tract and lungs, and a polymorphic leucocytosis.[6,10] Impairment of renal function and lesions in the glomeruli and convoluted tubules of the kidney of animals acutely poisoned with dimethylnitrosamine have also been observed.[9,10]

The chemically unstable nitrosamides, such as methylnitrosourea and methylnitrosourethane, have relatively little damaging action on the liver, and necrosis, when it occurs, is periportal rather than centrilobular. Nitrosamides cause local tissue injury of varying severity at the site of administration, and varying degrees of damage to distant organs. Methylnitrosourethane, for example, causes severe necrotic stomach lesions after oral intubation in the rat, and marked lung damage as well as local tissue injury after subsequent injection.[11] N-nitrosourea, after oral or parenteral administration, has induced effects on the bone marrow, lymphoid tissues, and the small intestine.[9,11]

The most probable explanation for the different patterns of acute cellular injury induced by N-nitroso compounds is that the compounds themselves are not responsible for the lesions, but that they give rise to biologically active metabolites. The distribution of lesions would then depend on the distribution of the administered compound and the rate and site of its decomposition. This connection between metabolism and biological action apparently applies not only to the acute toxic effects of the nitroso compounds

but also to their mutagenic and carcinogenic effects and to their teratogenic action.

7.2 CARCINOGENICITY

The N-nitroso compounds are a highly potent and versatile group of chemical carcinogens. Since Magee and Barnes first demonstrated the hepatocarcinogenicity of dimethylnitrosamine in rats, many more alkylnitrosamines have been found to induce tumors in various animal species at many different organ sites.[5] While the rat is the most frequently studied animal model, numerous other species including mice, rabbits, hamsters, guinea pigs, dogs, monkeys, birds, fish, and amphibia are susceptible to the carcinogenic action of N-nitroso compounds. Although there is no direct evidence that these compounds have produced cancer in humans, there is no reason to suspect that man is exempt from the carcinogenic action of these agents. Reportedly, some 80 N-nitrosamines and 23 N-nitrosamides have been tested in rats at various research laboratories. About 80 percent of the N-nitrosamines and almost all of the N-nitrosamides tested were carcinogenic (Table 7-2).

A marked organ specificity in the carcinogenic response has been observed with the two groups of N-nitroso compounds, as shown in Table 7-3. The N-nitrosamines exert a specific carcinogenic effect primarily in the liver, esophagus, respiratory system, and kidney; whereas the central and peripheral nervous system, the gastrointestinal tract, and kidney are the main target tissues for the N-nitrosamides. Apparently, the site of tumor induction by different N-nitrosamines is influenced by their chemical structure, e.g., the length of the alkyl chain.

Tumors of the esophagus are among the most common types of neoplasm occurring after treatment with N-nitrosamines,

Table 7-2. CARCINOGENICITY OF N-NITROSO COMPOUNDS IN RATS[12]

	Number of compounds tested	Carcinogenic	Non-carcinogenic
N-Nitrosamines	79	62	17
N-Nitrosamides	23	21	2

Table 7-3. LOCALIZATION OF TUMORS INDUCED BY N-NITROSO COMPOUNDS IN RATS[12]

Target organ	Number of N-nitroso compounds affecting target organ	
	N-nitrosamines	N-nitrosamides
Liver	35	2
Esophagus-pharynx	32	3
Nasal cavities	18	-
Respiratory tract	10	1
Kidney	8	9
Tongue	8	-
Forestomach	7	11
Bladder	4	1
Central and peripheral nervous system	2	9
Ear duct	2	1
Testis	1	-
Ovary	1	2
Mammary glands	1	1
Sites of injection	3	4
Intestine	-	7
Glandular stomach	-	6
Skin	-	3
Jaw	-	1
Uterus	-	2
Vagina	-	1
Haemopoietic system	-	2

particularly with asymmetric N-nitroso-methylalkylamines; the route of administration does not appear to be important, as these tumors are observed after either oral or systemic administration of the compounds.[13] This type of tumor is rarely seen with the N-nitrosamides. Dibutylnitrosamine and some of its metabolic oxidation products induce bladder cancer in rats, mice, guinea pigs, and hamsters after systemic administration[14]; and one nitrosamide, methylnitrosourea, also induces cancer of the bladder after its local application.[15] One of the most noteworthy examples of organ or species susceptibility is the induction of tumors of the brain, spinal cord, cranial, and peripheral nerves by N-acyl-N-alkylnitrosamines in various animal species. Druckrey et al. showed that a single subcutaneous injection of ethylnitrosourea (20 mg/kg) to newborn or 10-day-old rats induces an almost 100 percent incidence of malignant tumors of the nervous system, which show basic morphological features and location sites strikingly similar to those of human neoplasms of the nervous system.[16] Table 7-4 lists some N-nitroso compounds and possible sites of tumorigenicity.

The role of metabolism and possible mechanisms of biological action of N-nitroso compounds have been extensively reviewed.[6,8,10,12] Nitroso compounds are readily metabolized by animals and there is good correlation between their metabolism and tumor induction. As the result of several years of research, a biochemical pathway by which dialkylnitrosamines are metabolized was proposed. A few salient features have been drawn from the literature regarding this proposed pathway.[17]

Perhaps the most important concept in nitrosamine carcinogenesis is the fact that nitrosamines must be

Table 7-4. SITES OF TUMORS PRODUCED BY SOME N-NITROSO COMPOUNDS[18]

Site	Compound
Skin	Methylnitrosourea
Nose	Diethylnitrosamine
Nasal sinus	Dimethylnitrosamine
Tongue	Nitrosohexamethyleneimine
Esophagus	Methylphenylnitrosamine
Stomach	Ethylbutylnitrosamine
Duodenum	Methylnitrosourea
Colon	Cycasin
Lung	Diethylnitrosamine
Bronchi	Diethylnitrosamine
Liver	Dimethylnitrosamine
Pancreas	Nitrosomethylurethane
Kidney	Dimethylnitrosamine
Urinary bladder	Dibutylnitrosamine
Brain	Methylnitrosourea
Spinal cord	Nitrosotrimethylurea
Thymus	Nitrosobutylurea
Lymph nodes	Ethylnitrosourea
Blood vessels	Nitrosomorpholine

metabolically activated by the host before they can exert any carcinogenic effects. The ultimate carcinogen synthesized in vivo from nitrosamines can be one of several chemical species including nitrite, hydroxylamine, a hydrazine derivative, or an alkylating intermediate, possibly a diazoalkane or carbonium ion (Figure 7-1). Eight nitrosamines have been shown to be noncarcinogenic in test animals:

1. Diallylnitrosamine
2. Dicyclohexylnitrosamine
3. Diphenylnitrosamine
4. Dibenzylnitrosamine
5. Methyl-t-butylnitrosamine
6. Ethyl-t-butylnitrosamine
7. Proline ethylesternitrosamine
8. Trimethylenetriaminenitrosamine

The noncarcinogenicity of these compounds suggested that α carbon hydroxylation followed by diazoalkane formation may be one of the key reaction mechanisms for producing carcinogenic nitrosamine derivatives. With longer chain dialkylnitrosamines, β oxidation, ω, or ω_1 oxidation may occur in addition to α carbon hydroxylation. After oxidative monodealkylation by microsomal enzymes, the aldehyde generated is further oxidized to yield CO_2, while the monoalkylnitrosamine is thought to decompose to alkylating intermediates. Salient features of the above outlined reaction mechanism are summarized in Figure 7-2.

Further evidence for the importance of α carbon hydroxylation in relation to nitrosamine carcinogenesis comes from studies done with nitrosopiperidine, nitrosopyrrolidine, and substituted derivatives of the two. Blockage by methyl groups of one or more carbon atoms alpha to the nitroso function in nitrosopiperidine greatly reduced the

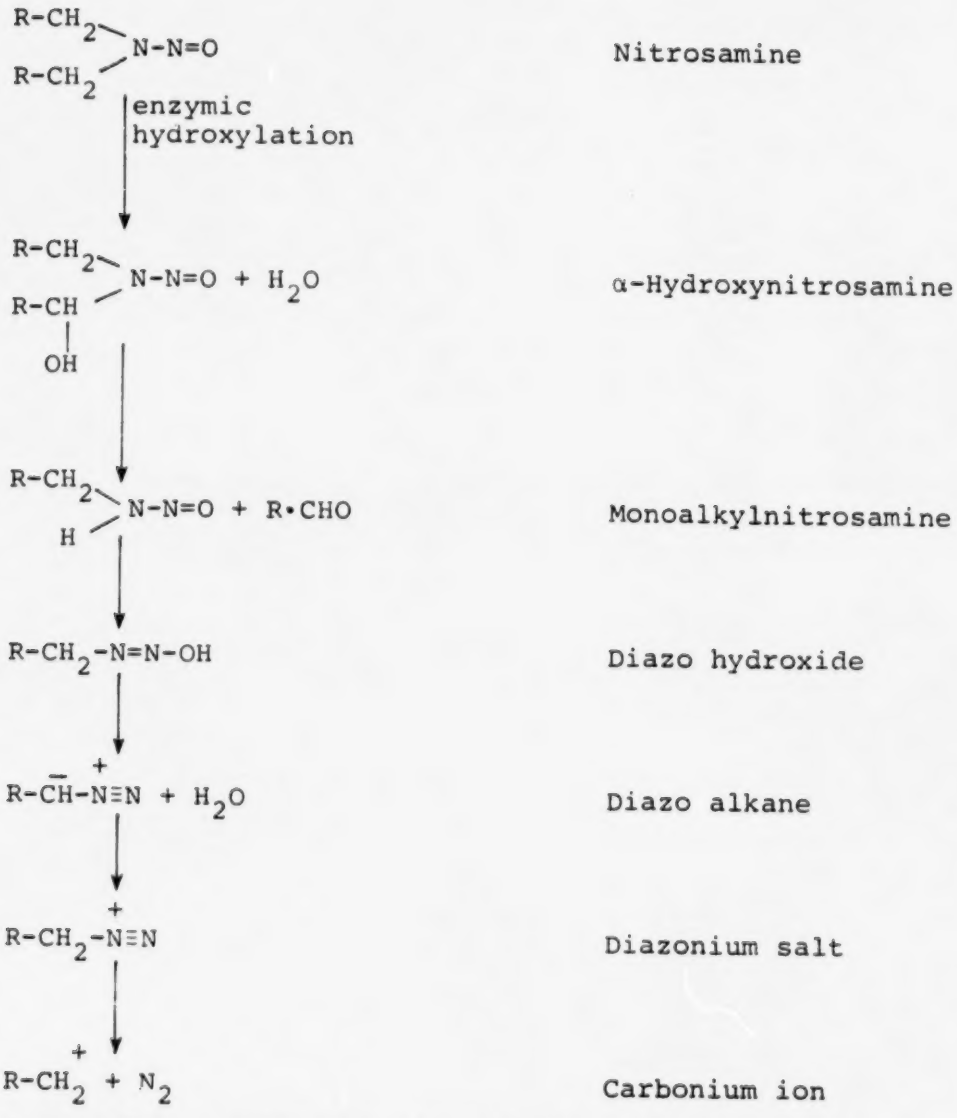


Figure 7-1. Transformation of nitrosamine to an active carcinogen[18]

A general scheme for the probable *in vivo* metabolic transformation is shown. The active alkylating agent may be the diazoalkane, the diazonium compound, or the carbonium ion. The R groups represent alkyl groups, usually methyl or ethyl. Dimethylnitrosamine is a potent carcinogen *in vivo*; the ultimate metabolic products would be methylating agents.

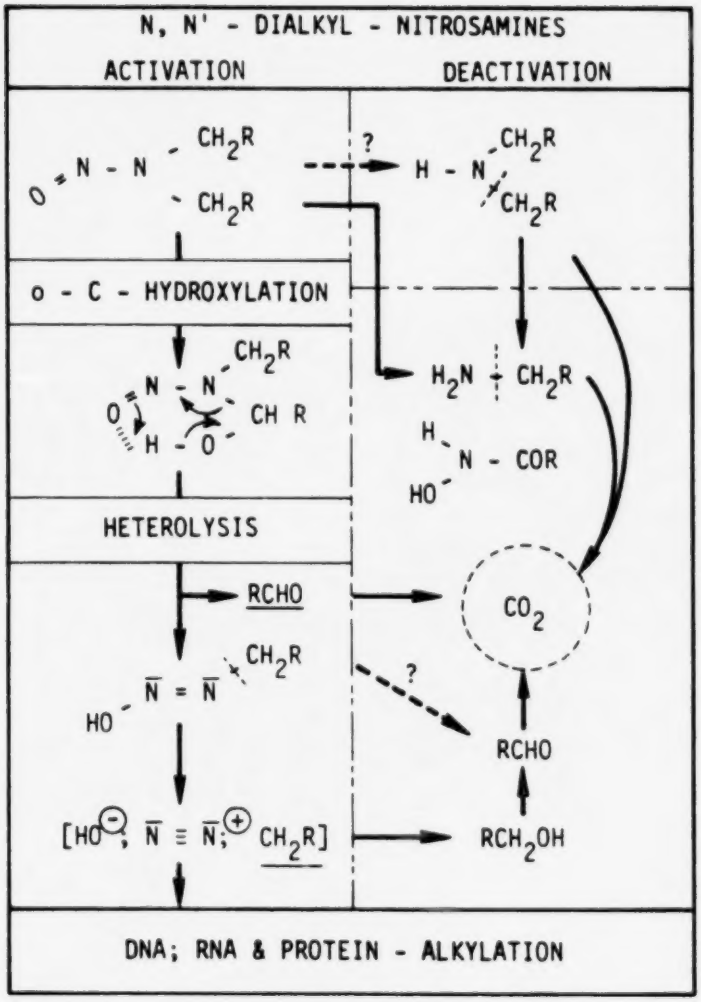


Figure 7-2. Metabolic activation (left side) and detoxification (right side) of N,N'-dialkylnitrosamines[12]

carcinogenicity of the derivative. Compared with 2-methyl, 3-methyl, or 4-methyl nitrosopiperidine, 2,6-dimethyl and 2,2,6,6-tetramethyl nitrosopiperidine were very weak carcinogens. In studies with nitrosopyrrolidine, it was determined that α methyl substitution significantly decreased liver carcinogenicity, while β chloride substitution changed the target organ and enhanced tumor lethality. Thus, for many nitrosamines, α carbon hydroxylation may be the critical initial in vivo reaction for determining ultimate carcinogenicity.

Several other nitrosamine structure-activity relationships are useful in predicting carcinogenicity. It has been shown that for a large number of nitrosamines the number of carbon atoms in the molecule is inversely proportional to the logarithm of (1/mean total carcinogenic dose). This relationship also predicts that a nitrosamine with greater than 14 carbon atoms is not likely to be strongly carcinogenic. Another useful correlation is the direct relationship between a nitrosamine's alkylating activity and its carcinogenicity.[17]

Neoplasms of offspring as a result of prenatal exposure to various N-nitrosamines and N-nitrosamides have been demonstrated in different animal species, including the rat, mouse, hamster, and pig (Table 7-5). The pregnant animals were treated by various routes of administration (oral, inhalation, intraperitoneal, subcutaneous, and intravenous), which were equally effective. The time of treatment during gestation, however, was a critical factor. In the rat, for example, these substances generally induce an embryotoxic effect when administered between days 1 and 10, a teratogenic effect between days 8 and 10, and a carcinogenic effect from day 10 to delivery.

Table 7-5. N-NITROSO COMPOUNDS AND RELATED SUBSTANCES INDUCING TUMORS FOLLOWING TRANSPLACENTAL EXPOSURE[6]

Compound	Species	Principal organs affected in the offspring
N-Nitrosodimethylamine	Rat	Kidney
	Mouse	Lung and liver
N-Nitrosodiethylamine	Rat	Kidney, mammary glands, nasal cavities, and thymus
	Mouse	Lung, liver, esophagus, and forestomach
	S.G. hamster	Trachea
N-Methyl-N-nitrosourea	Rat	Kidney and nervous system
	Mouse	Lung and liver
N-Ethyl-N-nitrosourea	Rat	Nervous system and kidney
	Mouse	Lung, liver, nervous system, and hematopoietic system
	S.G. hamster	Nervous system
	Pig	Sweat glands and skin
Ethylurea + sodium nitrite	Rat	Nervous system
N-Nitroso-N-n-propylurea	Rat	Nervous system
N-Ethyl-N-nitrosobiuret	Rat	Nervous system
N-Methyl-N-nitrosourethane	Rat	Kidney, nervous system, ovary, liver, mammary glands
Azoxymethane	Rat	Kidney, nervous system
1,2-Diethylhydrazine	Rat	Nervous system
1-Benzyl-2-methylhydrazine	Rat	Nervous system and kidney
Azoethane	Rat	Nervous system
Azoxyethane	Rat	Nervous system
1-Phenyl-3,3-dimethyltriazene	Rat	Nervous system and kidney
1-Phenyl-3,3-diethyltriazene	Rat	Nervous system
1-Pyridyl-3,3-diethyltriazene	Rat	Nervous system
N-Isopropyl-2-(methyl-hydrazine)-p-toluamide	Rat	Nervous system

Since many N-nitroso compounds require metabolic activation to exert their carcinogenic action, the lack of an adequate enzymatic system in the fetus during the first period of pregnancy may explain why no tumors were observed when the exposure was limited to this period. N-nitrosodimethylamine, azoxyurethane, and 1-phenyl-3,3-dimethyltriazene induced tumors in offspring only when administered during the last days of pregnancy.[6] Magee detected metabolic activation of N-nitrosodimethylamine in fetal rat tissues on the 21st day of pregnancy, but not on the 15th day.[19] Metabolic activation of ethyl derivatives of hydrazo-, azo- and azoxyalkanes and 1-aryl-3,3-dialkyl triazenes seems to occur at an earlier fetal stage than for the corresponding methyl derivatives.[20]

The sensitivity of the nervous system at various stages of prenatal development was studied by Ivankovic and Druckrey using the direct carcinogen N-ethyl-N-nitrosourea, which was administered to rats in single doses daily throughout pregnancy.[21] A high incidence of neurogenic tumors in offspring was observed when this carcinogen was administered on the 5th to 18th day of pregnancy or shortly before delivery, but not when it was administered before the 11th day. The sensitivity of the nervous system of prenatal rats was about 50 times higher than that of adult rats.[22]

7.3 SYNERGISTIC EFFECTS

There have been several reports in the literature of synergistic and modifying effects on nitrosamine carcinogenesis. Two recent examples involving respiratory and renal carcinogenesis illustrate this point. Montesano and Saffiotti have shown that systemic treatment of hamsters with a relatively low dose of diethylnitrosamine, which by itself would induce few, if any, tumors of the respiratory

tract, can greatly increase the incidence of respiratory tumors induced by subsequent treatment with a polycyclic hydrocarbon which also, by itself, would have very low carcinogenic activity.[23] It has also been demonstrated that intratracheal instillation of inorganic particulate matter, such as ferric oxide, can exert a similar synergistic action on diethylnitrosamine carcinogenesis. Swann and McLean have shown that the incidence of kidney tumors in the rat in response to a single dose of dimethylnitrosamine can be greatly increased by prior maintenance of the animals on a protein-deficient diet.[24] These and other examples of modifying effects on nitrosamine carcinogenesis may have important implications for human populations exposed to low levels of nitrosamines in the environment.

7.4 HUMAN HEALTH HAZARD[30]

A causal relationship between nitrosamines and human cancer is suggested by the following: (1) All mammals studied have been shown to be susceptible to tumor induction by at least one nitrosamine; (2) Nitrosamines (or their metabolites) are highly effective carcinogens by any route of administration (inhalation and oral intake included); (3) Some of the animal neoplasms induced by nitrosamines are predominantly epithelial and their organotypic and histologic features resemble those seen in humans; (4) Nitrosamines are metabolized *in vitro* similarly by human, guinea pig, and rat tissue; (5) Nitrosamines occur in the human environment e.g., in cured meat and fish products, tobacco and tobacco smoke, and ambient air; and (6) evidence is conclusive that nitrosamines or nitrosamides can be formed *in vivo*, most likely in the mammalian stomach or possibly in the lower gastrointestinal tract, through interaction of

secondary and tertiary amines ingested as food or drugs with nitrite, or as a result of microbial metabolism.

The cause and effect relationship between certain environmental and pharmaceutical chemicals, and the development of certain human neoplasms, has been shown. The incidence of cancer in man is quite high, and the distribution of cancers of certain types in some segments of the population seems to reflect well-defined exposures to carcinogens. Although the daily exposure of man to nitrosamines is unknown, nitrosamine precursors are ubiquitous in the environment. Continued chronic exposure to these nitrosamine precursors could conceivably result in the formation of nitroso compounds, and, even if such nitroso compounds were present at very low levels, unremitting insults from these compounds over several decades might contribute to human cancer. Moreover, the distinct possibility that other noxious or etiologic agents could act synergistically with nitrosamines to modify their biological effects should be considered. It should be noted in this discussion, however, that only a few nitrosatable precursors, and their respective nitrosamine derivatives, have been shown to induce neoplasms in laboratory animals.

7.5 MUTAGENICITY AND TERATOGENICITY

Many carcinogenic nitroso compounds are mutagenic and a few have been found to be teratogenic.[6,11,12,25] The nitrosamides include some of the most potent known chemical mutagens, e.g., N-methyl-N-nitrosoguanidine, and N-methyl-nitrosourea. As with acute toxicity, there is a clear distinction between the mutagenic actions of the nitrosamines and of the nitrosamides. The nitrosamides are powerfully mutagenic in all the usual microbial systems, in several plants and in Drosophila, but the nitrosamines are

active only in Drosophila.[6] This difference suggests that activation may be dependent on a metabolic system present in the insect that is absent in the microorganisms. This hypothesis is supported by the work of Malling, who demonstrated that N-nitrosodimethylamine is mutagenic when incubated with bacteria in the presence of rat liver microsomes.[26] The fact that several nitrosamines are actively mutagenic when tested by the host-mediated assay offers additional support.[27] In this procedure, test organisms are placed in the peritoneal cavity or elsewhere in the body, and the suspected mutagenic agent is injected by another route. The test indicates mutagenic activity in compounds which require metabolic activation in the body, but which are inactive when administered directly to the test organism.

The teratogenicity of nitrosocompounds has been much less extensively investigated. It is discussed briefly in the reviews by Magee[11] and Magee and Barnes.[25] As with transplacental carcinogenesis, the nitrosamides are active while the nitrosamines are not, except when administered late in pregnancy. N-nitrosomethylurea given to rats on the 13th or 14th day of gestation results in fetal deaths and resorption and deformities in progeny that reach term.[28] When N-nitrosoethylurea is administered to rats prior to day 12 of pregnancy, the compound is not carcinogenic but is powerfully teratogenic.[29] The difference in activity between the N-nitroso compounds is probably related to the capacity for direct action of nitrosamides and the lack of sufficient amounts of activating enzymes in the fetus until the last few days of pregnancy.

7.6 EPIDEMIOLOGY OF NITROSAMINES

In contrast to the vast number of cases of human blad-

der cancer attributable to aromatic amine exposure, there has not been one documented case of human cancer induced by nitrosamine exposure reported in the literature. However, there is epidemiological evidence linking conditions conducive to the *in vivo* or *in vitro* formation of nitrosamines with elevated rates of gastric cancer. Although this type of epidemiological evidence is insufficient to establish a cause and effect relationship, it does provide a conceptual framework for logical analysis of the possible public health hazards posed by environmental exposures to nitrosamines or their precursor compounds. For this reason, some of the studies showing plausible indirect associations between nitrosamine exposure and human cancer are summarized in detail as follow:

Correa *et al*. have proposed a model that explains the etiology of the type of human gastric cancer most influenced by environmental factors.[31] They postulate that the "intestinal type" of gastric carcinoma ultimately results from a series of mutations begun in the first decade of life, and the mutagenic agent involved could be a nitroso compound synthesized in the upper gastrointestinal tract by the action of nitrite on various nitrogen-containing compounds. Usually, these nitroso compounds do not penetrate the gastric epithelial cell, presumably because of an intact mucous barrier or inhibition of their synthesis by antioxidants present in food. The mucous barrier, however, may be overcome by irritants or abrasives, and once the first mutation occurs, the glandular gastric epithelium is gradually changed to intestinal-type epithelium, the mucous barrier altered, and the pH elevated. With this state of intestinal metaplasia, bacterial proliferation in the gastric cavity can facilitate the conversion of nitrates to nitrites. An elevated nitrite pool increases the possibil-

ity of forming carcinogenic nitroso compounds. After 30 to 50 years, this process of intestinal metaplasia eventually leads to a neoplastic transformation and the resulting invasive tumor in some individuals.

Zaldivare et al. showed a strong correlation between mean age-adjusted death rates for gastric cancer in Chile for 1960, 1962, and 1964 and exposure to sodium nitrate and total nitrates used as fertilizers.[32] The analysis was carried out using mortality, census, and fertilizer consumption data broken down by provinces. An index of general population exposure was obtained by dividing the metric tons of fertilizer consumed in each province by the number of persons in the province. The regression of gastric cancer death rates on the general population exposed to sodium nitrate showed a highly significant association ($p < 0.00005$). The equation of the regression line was:

$$(1) \quad y = 37.01 + 910.2X$$

where y equals the mean age-adjusted death rate per 100,000 population for stomach cancer, and X equals the metric tons of sodium nitrate consumed per person. A correlation coefficient of 0.745 was calculated for the fitted data. When gastric cancer death rates were regressed on the general population exposure to total nitrates, another significant association was found ($p < 0.0001$). The resulting equation was calculated to be:

$$(2) \quad y = 36.77 + 454.0X$$

where y equals the mean age-adjusted death rate per 100,000 population for stomach cancer, and X equals the metric tons of total nitrates consumed per person. A correlation coefficient of 0.718 was calculated for the fitted curve.

In certain areas of northern China, there is a very high incidence of esophageal cancer; in some communities it

ranks as the leading cause of death.[30] Food samples taken in these high-incidence areas contained significantly higher levels of dimethylnitrosamine, diethylnitrosamine, and methylphenylnitrosamine than those taken in low-incidence areas of the same general region. In addition, a fungus, Geotrichum candidum, which is known to act as a cocarcinogen with nitrosamines, was found in pickled vegetables commonly used as food in the high-incidence areas. Nitrosamines and their precursor compounds were also found in gastric fluid aspirated from noncancerous patients living in the same high-incidence areas. These studies in China suggest a relationship between cancer of the esophagus and the ingestion of food containing nitrosamines and a fungus that may serve as a cocarcinogen.

Other studies have implicated nitrosamine exposure as a possible cause of human cancers, but in some the link is tenuous. Weisberger et al. speculated that the decline in gastric cancer in the United States mortality in the last 40 years may be partially due to the more widespread use of refrigeration.[33] Their argument is based upon the fact that nitrate present in food can be reduced to nitrite when stored at room temperature and thus react with naturally occurring substances to form carcinogenic nitroso compounds. Another study in Africa attempted to link the ingestion of alcoholic beverages containing detectable levels of dimethylnitrosamine with high incidences of esophageal cancers.[34] Follow-up studies could not thoroughly substantiate the observed association, however.

REFERENCES

1. Barnes, J. M., and P. N. Magee. Some Toxic Properties of Dimethylnitrosamine. Brit. J. Ind. Med., 11:167, 1954. [cited in (4)]

2. Sakshaug, J., E. Sögnen, M. A. Hansen, and N. Koppang. Dimethylnitrosamine; Its Hepatotoxic Effect in Sheep and its Occurence in Toxic Batches of Herring Meal. Nature, 206:1261, 1965. [cited in (4)]

3. Ender, F., G. Havre, A. Helgebostad, N. Koppang, R. Madsen, and L. Ceh. Isolation and Identification of a Hepatotoxic Factor in Herring Meal Produced from Sodium Nitrite Preserved Herring. Naturwissenschaften, 51:637, 1964. [cited in (4)].

4. Magee, P. N. Toxicity of Nitrosamines: Their Possible Human Health Hazards. Fd. Cosmet. Toxicol, 9:207-18, 1971.

5. Magee, P. N., and J. M. Barnes. The Production of Malignant Primary Tumors in the Rat by Feeding Dimethylnitrosamine. Brit. J. Cancer, 10:114-22, 1956.

6. Magee, P. N., R. Montesano, and R. Prussmann. N-Nitroso Compounds and Related Carcinogens. In: Chemical Carcinogens, ACS Monograph 173. C.E. Searle (ed.), American Chemical Society, Washington, D. C. 1976. pp. 491-625.

7. Anonymous. Nitrosamines Can Be Easily Formed in Air, California Scientist Tells ACS. Toxic Materials News, 4(38):236, 1977.

8. Shank, R. C. Toxicology of N-Nitroso Compounds. Toxicol. Appl. Pharm, 31:361-368, 1975.

9. Magee, P. N., and P. F. Swann. Nitroso Compounds. Brit. Med. Bull., 25:240-244, 1969.

10. Magee, P. N., and R. Schoental. Carcinogenesis by Nitroso Compounds. Brit. Med. Bull., 20:102-106, 1964.

11. Magee, P. N. In Vivo Reactions of Nitroso Compounds. Ann. N. Y. Acad. Sci., 163:717-29, 1969.

12. Montesano, R., and H. Bartsch. Mutagenic and Carcinogenic N-Nitroso Compounds: Possible Environmental Hazards. Mut. Res., 32:179-228, 1976.

13. Druckrey, H., R. Preussmann, S. Ivankovic, and D. Schmähl. Organotrope Carcinogene Wirkungen bei 65 Verschiedenen N-Nitroso-Verbindungen an BD-Ratten. Z. Krebsforsch., 69:103-201, 1967. [cited in (12)]

14. Okada, M., E. Suzuki, J. Aoki, M. Ioyshi, and Y. Hashimoto. Metabolism and Carcinogenicity of N-butyl-N-(4-hydroxybutyl) nitrosamine and Related Compounds. In: Recent Topics in Chemical Carcinogenesis, Gann Monograph on Cancer Research No. 17, S. Odashima, S. Takayama and H. Sato (eds.), University of Tokyo Press, Tokyo, 1975. [cited in (12)]

15. Hicks, R. M., and J. St. J. Wakefield. Rapid Induction of Bladder Cancer in Rats with N-Methyl-N-nitrosaurea. I. Histology. Chem. Biol. Interactions, 5:139-52, 1972. [cited in (12)]

16. Druckrey, H., B. Schagen, and S. Ivankovic. Erzeugung Neurogener Malignome durch Einmalige Gabe von Athyl-nitrosoharnstoff (ANH) an Neugeborene und Junge BD-Ix Ratten. Z. Krebsforsch., 74:141-161, 1961. [cited in (12)]

17. Smith, J. A. Nitrosamine Structure-Activity Relationships. A Memorandum to C. Sawyer, PEDCo Environmental, Inc. May 27, 1977.

18. Goldstein, A., L. Aronaw, and S. M. Kalman. Chemical Carcinogenesis. In: Principles of Drug Action: The Basis of Pharmacology. 2nd edition. John Wiley and Sons, New York, 1974. pp. 667-702.

19. Magee, P. N. Mechanisms of Transplacental Carcinogenesis by Nitroso Compounds. In: Transplacental Carcinogenesis, International Agency for Research on Cancer, L. Tomatis and U. Mohr (eds.), IARC Scientific Publications, Lyon, 1973. pp. 143-48. [cited in (12)]

20. Druckrey, H. Chemical Structure and Action in Transplacental Carcinogenesis and Teratogenesis. In: Transplacental Carcinogenesis, International Agency for Research on Cancer, L. Tomatis and U. Mohr, (eds.), IARC Scientific Publications, Lyon, 1973. pp. 45-58. [cited in (12)]

21. Ivankovic, S., and H. Druckrey. Transplacentare Erzeugung Maligner Tumoren des Nervensystems. I. Athylnitroso-harnstoff (ANH) und BD Ix-Ratten. Z. Krebsforsch., 71:320-60, 1968. [cited in (12)]

22. Druckrey, H., R. Preussman, and S. Ivankovic. N-nitroso Compounds in Organotropic and Transplacental Carcinogenesis. Ann. N.Y. Acad. Sci., 163:676-96, 1969. [cited in (12)]

23. Montesano, R., and U. Saffiotti. Carcinogenic Response of the Respiratory Tract of Syrian Golden Hamsters to Different Doses of Diethylnitrosamine. Can. Res., 28:2197, 1968. [cited in (4)]

24. Swann, P. F., and A. E. M. McLean. The Effect of Diet on the Toxic and Carcinogenic Action of Dimethylnitrosamine. Biochem. J.: 107:14, 1968. [cited in (4)]

25. Magee, P. N., and J. M. Barnes. Carcinogenic Nitroso Compounds. Adv. Cancer Res., 10:163-243, 1967.

26. Malling, H. V. Muta. Res., 13:425, 1971. [cited in (6)]

27. Legator, M. S., and H. V. Malling. Chemical Mutagens: Principles and Methods for Their Detection. A. Hollaender (ed.), Plenum, New York, 1971. [cited in (6)]

28. Von Kreybig, T. Effect of a Carcinogenic Dose of Methylnitrosourea on the Embryonic Development of the Rat. Z. Krebsforsch., 67:46-50, 1965. [cited in (30)]

29. Napalkov, N. P., and V. A. Alexandrov. On the Effects of Blastomogenic Substances on the Organism During Embryogenesis. Z. Krebsforsch., 71:32-50, 1968. [cited in (30)]

30. Scientific and Technical Assessment Report on Nitrosamines. EPA-600/6-77-001, U.S. Environmental Protection Agency, Washington, D. C., 1976.

8.0 IDENTIFICATION OF POTENTIALLY HAZARDOUS, COMMERCIALLY SIGNIFICANT AMINES

8.1 MASTER LIST OF COMMERCIAL AMINE PRODUCTS

The master list of commercially significant industrial amines is compiled in its entirety in Appendix A. Both the Stanford Research Institute Directory of Chemical Procedures and the Internationl Trade Commission Report[1] were used as resources to compile the list. The exact definition by which amine chemicals were chosen for the master list is as follows.

"Those compounds derived from ammonia in which the hydrogen atoms are replaced by one, two, or three alkyl or aryl groups" (2). Alkyl groups are hydrocarbon radicals based on alkanes (e.g. butane), and aryl groups are hydrocarbon radicals based on benzene). Although saturated nitrogen ring compounds are sometimes considered amines, such compounds are normally treated under the category of heterocyclic compounds. This definition eliminates heterocyclics, amides, imides, oximes, azo and diazo compounds, imines (in which the nitrogen is attached to one carbon atom), nitriles, quaternaries, hydrazines, salts, lactams, amine oxides, and amidines. Nitrogen-ringed compounds (triazole, thiazole, thiazoline, and numerous others) with an $-NH_2$ group attached to a ring carbon which attached to a nitrogen by a double bond represent basically amidine likeages ($H_2N - C' = N$); and such compounds are not classed as amines for present purposes.

All the amine chemicals are listed alphabetically by amine classification (primary, secondary, and tertiary) and

under specific industry heading categories as delineated in Table 8-1. The lists comprise over 1900 chemicals from these two resources. All of the classification and sorting was done by hand with a computerized alphabetical sort routine used to print out those amines by classification and industry type. The Organic Dyes and Pigments Industry was the most difficult to categorize and classify. An attempt was made to name those dyes and pigments for which only structures are given in the Color Index. This, however, was highly time consuming and was not completed. The dyes and pigments that are included do fit the amine definition and contain a Color Index Number, compound name (if known), and an (*) to identify whether it was listed in the U.S. Environmental Protection Agency report on organic dyes and pigments.[2]

8.2 SUBSET LIST OF POTENTIALLY HAZARDOUS AMINE CHEMICALS

The master list of commercially significant amines (Appendix A) was reviewed very carefully in terms of identifying a subset list of amines chosen according to the following criteria:

- Produced in high volumes
- Potentially react to form toxic chemicals, e.g., Nitrosamines
- Produces potentially chronic or acute toxicity in humans

Table 8-2 summarizes those amines known to be produced as high-volume chemicals. A computerized search technique using Medline, Toxline, and APTIC toxic chemicals data base services was used to generate a list of amine derivative chemicals whose health effects are a subject of concern (Table 8-3). Those amine chemicals coming under close surveillance by the International Association for Research

Table 8-1. INDUSTRY CATEGORIES OF CLASSIFIED INDUSTRIAL AMINE CHEMICALS

- Acids, fatty and higher synthetics[a]
- Alcohols, fatty and higher synthetics[a]
- Chelating agents
- Crude products from petroleum and natural gas[a]
- Cyclic intermediates
- Elastomers[b]
- Enzymes[c]
- Fibers, synthetic[b]
- Flavor and perfume materials
- Medicinal chemicals[d]
- Miscellaneous chemicals
- Organic dyes and pigments[e]
- Pesticides
- Plasticizers[a]
- Plastics and resins[b]
- Rubber processing chemicals
- Surface active agents
- Tar and tar crudes[a]

[a] Contains no amine chemicals according to the established definition.

[b] Basically polymeric chemicals containing nitrogen. It is not an amine-type linkage.

[c] All in this category are primary amines; because of their low annual manufactured volumes, individual enzymes are not listed.

[d] Amine compounds under this category are regulated under Food and Drug laws and are not addressed by this study.

[e] Identified by Colour Index No. and named where known.

Table 8-2. LIST OF HIGH VOLUME INDUSTRIAL AMINES

1. m-Aminobenzoic acid (primary)
2. p-Aminobenzoic acid (secondary)
3. Aminoethylethanolamine (primary and secondary)
4. p-Aminophenol (primary)
5. Amylamine (primary)
6. Aniline (primary)
7. m-Anisidine (primary)
8. o-Anisidine (primary)
9. p-Anisidine (primary)
10. Benzylmine (primary
11. n-Butylamine (primary)
12. sec-Butylamine, mono (primary)
13. Tert-Butylamine (primary)
14. m-Chloroaniline (primary)
15. o-Chloroaniline (primary)
16. p-Chloroaniline (primary)
17. Cyclohexylamine (primary)
18. 3,4-Diaminobenzoic acid (primary)
19. 3,5-Diaminobenzoic acid (primary)
20. 2,4-Dichloroaniline (primary)
21. 2,5-Dichloroaniline (primary)
22. 3,4-Dichloroaniline (primary)
23. Dicyclohexylamine (secondary)
24. Diethylamine (secondary)
25. Dimethylamine (secondary)
26. N,N-Dimethylaniline (tertiary)
27. Diphenylamine (secondary)
28. Ethanolamine, mono (primary)
29. Ethanolamine, di (secondary)
30. Ethanolamine, tri (tertiary)
31. Ethylamine (primary)
32. Ethylenediamine (primary)
33. Glycine (primary)
34. Hexamethylenediamine (primary)
35. Isopropylamine (primary)
36. Metanilic acid (primary)
37. Methylamine (primary)
38. N-Methylaniline (secondary)
39. Methylenedianiline (secondary)
40. o-Nitroaniline (primary)
41. p-Nitroaniline (primary)
42. o-Phenetidine (primary)
43. p-Phenetidine (primary)
44. Phenylanthranilic acid (secondary)
45. Propylamine (primary)
46. Tetramethylenediamine (primary)
47. Tetramethylethylenediamine (tertiary)
48. m-Toluidine (primary)
49. o-Toluidine (primary)
50. p-Toluidine (primary)
51. Toluidines, mixed (primary)
52. Triethylamine (tertiary)
53. Trimethylamine (tertiary)
54. 2,3-Xylidine (primary)
55. 2,4-Xylidine (primary)
56. 2,5-Xylidine (primary)
57. 2,6-Xylidine (primary)
58. 3,4-Xylidine (primary)
59. Xylidine, mixed isomers (primary)

(continued)

Table 8-2 (continued).

60.	Ethylenediaminetetraacetic acid (EDTA) (tertiary)
61.	Methionine (primary)
62.	Anthranilic acid (primary)
63.	Toluene-2,4-diamine (primary)
64.	Sulfanilic acid (primary)
65.	Tri-n-butylamine (tertiary)
66.	Tripropylamine (tertiary)
67.	2-Dimethylaminoethanol (tertiary)
68.	Di-n-butylamine (secondary)
69.	Diisopropylamine (secondary)
70.	Di-n-amylamine (secondary)
71.	Di-n-propylamine (secondary)
72.	Tetraethylenepentamine (primary and secondary)
73.	Triethylenetetramine (primary and secondary)
74.	Ethylethanolamine (secondary)
75.	Sarcosine (secondary)
76.	Diisopropanolamine (secondary)
77.	Diethylenetriamine (primary and secondary)
78.	Isobutylamine (primary)
79.	N-Aminoethylpiperazine (primary)
80.	N-Ethylaniline (secondary)
81.	N,N-Diethylaniline (tertiary)
82.	tert-Octylamine (primary)

Based on review of resource information from: 1) Organic Tariif Commission Report, and 2) Star document Amine/ Nitrosamine Assessment Study.

Table 8-3. LIST OF AMINE DERIVATIVE CHEMICALS WITH POSSIBLE ADVERSE HEALTH EFFECTS[a]

1.	Ethambutol (secondary)
2.	Aminopyrene (primary)
3.	Oxytetracycline (tertiary)
4.	Chlorpromazine (tertiary)
5.	Dextropropoxyphene (tertiary)
6.	Chlorheniramine (tertiary)
7.	Methadone (tertiary)
8.	Methapyrilene (tertiary)
9.	Quinacrine (secondary and tertiary)
10.	Lucanthone (secondary and tertiary)
11.	Trimethylamine (tertiary)
12.	2-Dimethylaminoethanol (tertiary)
13.	N,N-Dimethylglycine methyl ester (tertiary)
14.	N,N-Dimethylglycine (tertiary)
15.	Triethanolamine (tertiary)
16.	Nitrilotriacetic acid (tertiary)
17.	N,N-Dimethyldodecylamine (tertiary)
18.	Pyribenzamine (tertiary)
19.	Isoprenaline (secondary)
20.	Phenylenediamine (primary)
21.	p-Nitrosodimethylaniline (tertiary)
22.	p-Nitrosodiethylaniline (tertiary)
23.	4,4-Diaminodiphenyl methane (primary)
24.	o-Toluidine (primary)
25.	4,4-Methylene-Bis-(2-chloroaniline) (primary)
26.	Phenoxybenzamine (tertiary)
27.	2-Naphthylamine (primary)
28.	Benzidine (primary)
29.	Ca-DTPA (tertiary)
30.	Aminobiphenyl (primary)

(continued)

Table 8-3 (continued).

31.	Hycanthone (secondary and tertiary)
32.	3,3-Dichlorobenzidine (primary)
33.	4-Aminophenyl (primary)
34.	2-Aminophenyl (primary)
35.	α-napthylamine (primary)
36.	β-napthylamine (primary)
37.	4,4-Methylene Bis (2-methylaniline) (primary)
38.	Trans-2-(Dimethylamino) methylimino-5-2-nitro-2-Furyl) Vinyl-1,3,4-oxadiazole (tertiary)
39.	para Amino Azo Benzene (primary)
40.	p-Dimethylamino Azo Benzene (tertiary)
41.	o-Amino Azo Toluene (primary)

[a] Generated from a computerized toxic effects data base search.

on Cancer (IARC) are listed in Table 8-4. Not all these chemicals are currently being produced in the United States, but their overriding carcinogenicity risk requires their listing in an subset list of hazardous amine chemicals. A subset list of potentially hazardous amine chemicals was compiled after close inspection of those chemicals delineated in Tables 8-2 to 8-4 and on the master list of commercially significant amines (Table 8-5). The rationale for selecting these (46) chemicals is also included in the table, along with a classification of whether the amine chemical is primary, secondary, or tertiary. Only secondary and tertiary amines can react to form nitrosamines, and these, as listed, satisfy the second criterion for the subset list development.

Table 8-6 provides a comparison of the subset list candidates with other published lists containing amine derivative chemicals commensurate with our definition. The sources of these lists are explained under footnotes a to i on the table.

8.3 SELECTION OF SITES FOR INVESTIGATION

After development of the list of key amines shown in Table 8-5 and its comparison with similar lists developed for other purposes, efforts were made to identify localities where their production and usage might result in elevated cancer rates. In the course of this investigation, only those 32 products marked with an asterisk were investigated before sites for further study were identified. To begin, facilities were identified that for 25 years have continuously produced at least one of the 32 key amines marked with an asterisk in Table 8-5. Development of the final list of amine manufacturing facilities required a four-step procedure described below:

Table 8-4. CARCINOGENIC AMINES LISTED IN THE IARC[a] MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN

Compound	Production volume, uses, and of sites
1. Auramine	° Dye and antiseptic
2. 4-Aminobiphenyl	° Manufactured in United States at one site from 1935-1955; rubber antioxidant
3. Benzidine	° Millions of pounds formerly produced per year in United States; more than 250 dyes derived from benzidine
4. o-Tolidine	° 243×10^3 lbs (1962); 95 dyes derived from o-Tolidine
5. o-Dianisidine	° 167 mt (1967), five sites; dye intermediate
6. 3,3'-Dichlorobenzidine	° 1600 mt (1971), five sites; dye intermediate
7. Magenta	° 53 mt (1964), five sites; dye
8. 4,4'-Methylene Bis (2-chloroaniline)	° 3500 mt (1972), two sites; used for curing liquid-castable polyurethane elastomers
9. 4,4'-Methylene-dianiline	° 700 mt (1966), three sites; used to manufacture isocyanates for manufacture of rigid polyurethane foam
10. 2-Naphthylamine	° 581 mt (1955), four sites; intermediate in manufacture of dyes and antioxidants
11. N,N-Bis(2-chloroethyl)-2-Naphthylamine	° Medicinal

[a] IARC = International Association for Research on Cancer.

mt = Metric tons

Table 8-5. ENVIRONMENTALLY HAZARDOUS INDUSTRIAL AMINE COMPOUNDS

Compound (amine classification)	Rationale
1. Auramine (tertiary)	° Human carcinogen ° Volume ° Uses
2. Benzidine (primary)	° Human carcinogen ° TLV considerations[a]
3. B-Naphthylamine (primary)	° Human carcinogen ° Volume ° TLV considerations
4. 4-Aminobiphenyl (primary)	° Human carcinogen ° TLV considerations
5. N,N - Bis (2-chloroethyl) 2-naphthylamine (tertiary)	° Human carcinogen
6. 4,4 -Methylenedianiline (primary)	° Carcinogen ° Volume 700 mt[b] ° (1966), three sites
7. 3,3 - Dichlorobenzidine (primary)	° Carcinogen ° TLV considerations ° 1600 mt (1971), three sites
8. 4,4 - Methylene Bis (2-Chloroaniline) (primary)	° Carcinogen ° TLV considerations ° 3500 mt (1972), two sites
9. o-Tolidine (primary)	° Carcinogen
10. Magenta (primary)	° Carcinogen ° 53 mt (1964), five sites
11. s-Dianisidine (primary)	° Carcinogen ° 160 mt (1967), five sites
12. Anthranilic acid (primary)	° Volume ° OTS Carcinogen code 3102[c]

(continued)

Table 8-5 (Continued).

Compound	Rationale
13. Toluene 2,4-diamine (primary)	° Volume ° OTS carcinogen code 4112
14. Dimethylamine (secondary)	° Volume ° Carcinogenic NA[d]
15. Ethylenediamine (primary)	° Volume ° TOSCA list of 300
16. Hexamethylenediamine (primary)	° Volume ° TOSCA list of 300
17. Toluidine (primary)	° Volume ° OTS carcinogen code 4111
18. Diethylamine (secondary)	° Volume ° Carcinogenic NA
19. Trimethylamine (tertiary)	° Volume ° Carcinogenic NA
20. Di-n-butylamine (secondary)	° Volume ° Carcinogenic NA
21. Di-n-amylamine (secondary)	° Volume ° Carcinogenic NA
22. Di-n-propylamine (secondary)	° Volume ° Carcinogenic NA
23. Anisidine (primary)	° Volume ° TLV consideration ° OTS carcinogen code 4111
24. m-Aminobenzoic Acid (primary)	° Volume ° OTS carcinogen code 4111
25. Diisopropylamine (secondary)	° Volume ° Carcinogenic NA
26. Diisopropanolamine (secondary)	° Volume ° Carcinogenic NA

(continued)

Table 8-5 (Continued).

Compound	Rationale
27. N-Methylaniline (secondary)	° Volume ° Carcinogenic NA
28. Diethanolamine (secondary)	° Volume ° Carcinogenic NA
29. Sarcosine (secondary)	° Volume ° Carcinogenic NA
30. Triethylamine (tertiary)	° Volume ° Carcinogenic NA
31. Tri-n-butylamine (tertiary)	° Volume ° Carcinogenic NA
32. Tripropylamine (tertiary)	° Volume ° Carcinogenic NA
33. Aniline (primary)	
34. Monoethanolamine (primary)	
35. Triethanolamine (tertiary)	
36. Methylamine (primary)	
37. N,N-Dimethylaniline (tertiary)	
38. Diphenylamine (secondary)	
39. p-Aminophenol (primary)	
40. o-Chloraniline (primary)	
41. Cyclohexylamine (primary)	
42. 3,4-Dichloroaniline (primary)	
43. Ethylamine (primary)	
44. Isopropylamine (primary)	
45. p-Nitroaniline (primary)	
46. Xylidines (primary)	

[a] TLV = Threshold limit value.

[b] mt = Metric tons.

[c] OTS = Office Toxic Substances.

[d] NA = Nitrosamines.

Table 8-6. ENVIRONMENTALLY HAZARDOUS INDUSTRIAL AMINES (46) LIST COMPARISON WITH OTHER PUBLISHED OR DEVELOPED LISTS

	a	b	c	d	e	f	g	h	i
	List of 46	Master list (~ 1200)	Industrial (82)	Star list	Health effects (41)	TSCA amines	N.J. EPA Carcinogens	IARC	TLV
* Auramine (T)	X						X	X	
* Benzidine (P)	X	X			X		X	X	X
* B-Naphthylamine (P)	X				X		X	X	X
* 4-Aminobiphenyl (P)	X				X	X	X	X	X
* N,N-Bis (2-chloroethyl) 2-naphthylamine (T)	X					X		X	
* 4,4- Methylene-dianiline (P)	X	X	X				X	X	
* 3,3- Dichloroben-zidine (P)	X				X		X	X	X
* 4,4- Methylene Bis (2-chloroaniline) (P)	X	X			X		X	X	X
* o-Tolidine (P)	X							X	
* Magenta (P)	X						X	X	
* o-Dianisidine (P)	X					X		X	
* Anthranilic acid (P)	X					X			
* Toluene-2,4-diamine (P)	X	X	X			X	X		
* Dimethylamine (S)	X	X	X	X		X			X
* Ethylenediamine (P)	X	X	X	X		X			X
* Hexamethylenediame (P)	X	X	X	X		X			
* Toluidine (P)	X	X	X			X			
* Diethylamine (S)	X	X	X		X	X			X
* Trimethylamine (T)	X	X	X	X		X			X
* Di-n-butylamine (S)	X	X	X	X	X				
* Di-n-amylamine (S)	X	X	X	X					
* Di-n-propylamine (S)	X	X	X						
* Anisidine (P)	X	X	X	X					X
* m-Aminobenzoic acid (P)	X	X	X			X			
* Diisopropylamine (S)	X	X	X						X
* Diisopropanolamine (S)	X	X	X						
* N-Methylaniline (S)	X	X	X						X

(continued)

Table 8-6 (continued)

	a	b	c	d	e	f	g	h	i
	List of 46	Master list (~1400)	Industrial (82)	Star list	Health effects (41)	TSCA amines	N.J. EPA Carcinogens	IARC	TLV
* Diethanolamine (S)									
* Sarcosine (S)									
* Triethylamine (T)									
* Tri-n-butylamine (T)									
* Tripropylamine (T)									

[a] PEDCo list of hazardous amines.

[b] Master list of commercially significant amines generated from a composite analysis of the Organic Tariff Commission Report and the SRI Directory according to a prescribed amines definition.

[c] Subset list of (82) high-volume, multiple-usage amine chemicals.

[d] Scientific and Technical Assessment Report on Nitrosamines, U.S. EPA, Research Triangle Park, North Carolina.

[e] Computerized search list for known toxic health effects of amine chemicals.

[f] Toxic Substances Control Act (1977) amine chemicals listed on the TOSCA 300 chemicals list.

[g] New Jersey list of potential chemical carcinogens.

[h] International Association for Cancer Research list.

[i] Threshold limit value.

Step 1: Identify companies producing amines before 1950.

Companies producing any of the list of 32 amines before 1950 were identified in the Thomas Register. Companies were listed separately for each of the 32 chemicals, and their production was confirmed from the 1938, 1940, 1945, and 1950 editions of the Thomas Register. All new companies found in the editions subsequent to 1938 were added to the list. Table 8-7 lists the amines known to have been commercially produced before 1950, together with their manufacturers.

Step 2: Confirm 25-year production.

Companies listed under the amines shown in Table 8-6 were checked in the 1969 and 1975 editions of the Thomas Register. Each company that reappeared was noted, but no new ones were added to the list. Since many facilities changed hands during the 25-year period, Moody's Industrials (published by Moody's Investor Services) was used to trace mergers and sales. Also, companies that ceased to appear in the Thomas Register were checked in the Moody's Industrials for any transaction with companies appearing in the list of manufacturers for that year.

Step 3: Locate amine manufacturing facilities.

Each facility showing 25 or more years of production was cross-checked in the SRI Directory of Chemical Producers, 1977 edition, to determine which plants still produce amines.

Appendix B presents the matrix of 32 amines, facilities producing them, and the historical record (1935 to 1977) of their production. The resulting confirmed list is shown in Table 8-8.

Step 4: Verify selected sites.

Prior to completing the list of producers, verification was needed that each plant had indeed produced the amine of

Table 8-7. AMINE CHEMICALS AND LONG-TERM MANUFACTURERS

Amine	Manufacturers
Anisidine	Monsanto
Anthranilic acid	Ciba
Cyclohexylamine	Monsanto
Benzidine	J.T. Baker
Diethanolamine	Carbide and Dow
Diethylaniline	Dow
Diisopropanolamine	Carbide
Diisopropylamine	CSC
Dimethylamine	CSC and Rohm
Dimethylaniline	Calco, J.T. Baker, and National Aniline
Ethanolamines	Carbide, Dow, Republic Chems.
Methylamines	CSC, Rohm (MDT)
B-Naphthylamine	National Aniline
o-Chloroaniline	Monsanto
p-Nitroaniline	Calco, Sherwin-Williams
Toluidine	National Aniline, Sherwin

Table 8-8. RESULTS OF SITE VERIFICATION CONTACTS

Company	Predicted amine manufacturing site	Site confirmed	Predicted amine product slate	Product confirmed
J.T. Baker Chemical Co.	Phillipsburg, N.Y. Warren County - 34041		Benzidine N,N-dimethylaniline	
Ciba-Geigy	McIntosh, Ala. Washington County - 01129		Anthranilic acid	
Commercial Solvents Corp.	Terre Haute, Ind. Vigo County - 18167		Monomethylamine Dimethylamine Trimethylamine Diisopropylamine	
Calco Chemical Co. (now American Cyanamid)	Bound Brook, N.J. Somerset County - 34035		N,N-dimethylaniline p-nitroaniline	
Union Carbide	Taft, La. St. Charles County - 22089		Diisopropanolamine Diethanolamine Triethanolamine Monoethanolamine	
Dow Chemical Co.	Freeport, Tex. Brazoria County - 48039		Monoethanolamine Diethanolamine Triethanolamine	
Allied Chemical (now Buffalo Color)	Buffalo, N.Y. Erie County - 36029		N,N-Dimethylaniline B-Naphthylamine Xylidine Benzidine	
Monsanto Co.	St. Louis, Mo. City of St. Louis - 29189		Anisidine o-Chloroaniline Cyclohexylamine	
	Sauget, Ill. St. Clair County - 17163		Anisidine o-Chloroaniline Cyclohexylamine p-Nitroaniline	
	Luling, La. St. Charles County - 22089		Anisidine o-Chloroaniline Cyclohexylamine	
E.I. DuPont de Nemours and Co., Inc.[a]	Deepwater, N.J. Salem County - 34033		N.A.	
	Belle, W. Va. Kanahwa County - 54039		N.A.	
	LaPorte, Tex. Harris County - 48201		N.A.	

[a] DuPont refused to release any information to us, but literature indicates that they have produced amines since the 1920's or 1930's at one or more of these sites.

N.A. - Not applicable.

concern for 25 years and that our county location for that plant was correct. This phase was executed by mail and telephone calls.

A procedure similar to that above was used to identify nitric acid plants in the 13 counties associated with production or use of amines. This subset of counties was used in the epidemiological analysis.

REFERENCES

1. U.S. International Trade Commission, Synthetic Organic Chemicals, United States Production and Sales, 1974 U.S. GPO, Washington, D.C., 1976.

2. Rose, A., and E. Rose. The Condensed Chemical Dictionary, 7th ed. Reinhold Book Corp. New York, N.Y., 1966.

3. Radian. End Use Patterns for Significant Organic Chemicals, EPA Contract No. 68-02-1319, Task 61, July 1976.

9.0 RETROSPECTIVE EPIDEMIOLOGICAL ANALYSIS

9.1 SELECTION OF CANCER TYPES FOR STUDY

The health effects data presented earlier were evaluated to identify potential causal relationships to relate specific chemical exposure with organ-specific cancers. This evaluation serves to focus the epidemiological analysis to be presented in this section. Organ-specific cancer associations must be developed prior to interpreting the cancer mortality rate results from the epidemiology analysis so that the number of spurious relationships may be reduced. Due to the large number of known and suspected sources of environmentally induced cancer, causal relationships are difficult to develop unless specific organ sites can be identified.

The relationship between aromatic amine exposure and the incidence of bladder cancer is quite well established. This organ-specific response is striking in man. Liver tumors are also associated with aromatic amine exposure in a number of animal species.

The relationship between nitrosamine exposure and cancer is much less clear, since conclusive evidence has been reported in the literature. Elevated gastric cancer rates, however, have been linked with nitrosamine exposure. Animal studies suggests that nitrosamines are highly carcinogenic by any route of administration; they appear to be metabolized similarly by man. Based on the carcinogenic response in rats, the evidence is that N-nitrosamines exert

a specific carcinogenic effect primarily in the liver, esophagus, respiratory system, and kidneys. The pancreas and other organs have also been reported to be the site of tumors produced by nitrosamine exposure. The central and peripheral nervous system, the gastrointestinal tract, and kidneys are the main target tissues for the N-nitrosamides. Due to their ubiquitousness in the environment and their ability to be formed in vivo, nitrosamines may be responsible for more than just gastric cancer.

The literature suggests that bladder cancer and cancer of the stomach and intestines are the most causally related to nitrosamine and aromatic amine exposure. There is evidence, as cited above, that specific organs may be involved and for purposes of this study cancer of the bladder, stomach, liver, esophagus, kidneys, and pancreas were designated as "selected cancers" whose incidence would be used for evaluation of possible influence of amine or nitrosamine exposure. Lung cancer was excluded from "selected cancers" because of its high incidence and possible connection with other causes, such as smoking, but was used as a basis for comparison of frequency with other types of cancer.

9.2 GENERAL METHODOLOGY

This element of the overall analysis identifies potential causal associations at locations processing key chemicals of interest that show elevations in specific cancer mortality rates. To allow an adequate latency period for potential tumor development, this analysis is restricted to counties with facilities manufacturing these chemicals for at least 25 years.

The major steps in this analysis are:

1. Identify organ-specific cancer types to screen for county elevations as discussed above.

2. Choose counties for epidemiological analysis as discussed in Section 8.0.

3. Determine the organ-specific mortality rates of the designated counties relative to their contiguous counties.

4. Determine the organ-specific mortality rates and any rate elevation for each designated county relative to the corresponding national rates for further epidemiological analysis.

5. Compare the cancer rates from the two analyses (Steps 3 and 4) to identify consistent trends.

6. Identify subsets of plants that produce(d) or use(d) specific chemicals or precursors of specific chemicals that are associated with the induction of any of the key organ-specific cancers identified in Step 1.

7. Determine if some of the county-specific mortality rates could be at least partially explained by confounding variables, such as higher degree of urbanization or industrialization, than the contiguous counties or the national average.

8. Using the above analyses, identify the counties with the most consistent and elevated organ-specific cancer rates. The plants in these counties would then be considered for a more rigorous analysis.

The two epidemiological comparisons are used since they tend, in part, to complement one another. Comparisons with national cancer rates provide a large population reference group with fairly reliable mortality rates for specific cancers. Although few potentially confounding variables are controlled, elevated cancer mortality rates can be detected. The national comparison strengthens the contiguous county analysis in cases where there are marked differences between a county compared with its contiguous counties. Important

differences include the degree of industrialization and the degree of urbanization or population density. In these cases, national comparisons serve to clarify mortality trends. For example, occupationally related cancers have less impact, especially for female comparison. The contiguous county comparisons provide some control for differences in environmental factors such as lifestyle and cultural makeup (since a similar ethnic composition often exists in a local area), drinking water source, and dietary habits.

9.3 EPIDEMIOLOGICAL ANALYSIS OF INDUSTRIAL AMINES

This section presents a systematic evaluation of the epidemiological analysis of cancer mortality rates associated with amine production. Thirteen counties were included, based on their identification in Section 8.0, as containing facilities producing or using one or more subsets of significant amines for more than 25 years. Appendix C contains site-evaluation data for these counties, including known historical amines production information, maps, and populations of the counties and their contiguous counties, and sex-specific cancer mortality data compared with national rates. The cancer types presented are: esophagus, stomach, liver, pancreas, kidney, bladder, lung, and total cancer. The mortality rates are deaths per 100,000 population. As can be seen from the U.S. rate, there are large rate differences between cancers and also by cancer type between males and females. Although some relationship might exist between lung cancer mortality and nitrosamine exposure, the high current lung cancer rate, especially for males, makes causal relationships very difficult to detect. Thus, lung cancer was not included in more detailed analyses.

The U.S. cancer mortality reveals that the female rate for all cancers is 75 percent of the male rate and occurs at a significantly lower relative rate for some of the cancers of interest in this analysis. For example, the female bladder cancer rate is only 35 percent of the rate among males. Due to lower female cancer rates and less occupationally related cancer, elevated rates among women are more readily detected and are less likely to be masked by occupational exposures. Hence, in this study, most comparisons consider data for both males and females. The cancer rate indices used for comparison are defined along with other terms used in the study in Table 9-1. Of the statistics derived from the computations for point-source analysis described in Appendix C, attention was focused upon the relative risk. These relative rate data were used together along with absolute cancer rates and relative risk data developed by the National Cancer Institute (NCI) for comparison of the incidence of specific cancers. The cancer types chosen for screening were bladder, esophagus, stomach, liver, kidney, pancreas, and total cancer. Bladder cancer is used to screen for aromatic amines, and the other organ-specific cancers are used to identify nitrosamines associated elevations. Since many environmental factors affect the incidence of cancer, amine/nitrosamine exposure may not account for a large portion of most cancer mortality rates. To aid in the comparisons, what has been termed "adjusted relative risk" was introduced. This is the relative risk value from NCI data for specific cancer types divided by the relative risk value for all cancer. For example, the relative risk for bladder cancer in women in Erie County, New York, is 124.7; the relative risk for all cancer in women is 109.4. The adjusted relative risk is 124.7 ÷ 109.4 or 1.25. The two indices indicate bladder cancer in women is 24.7

TABLE 9-1. LIST OF TERMS ASSOCIATED WITH CANCER INCIDENCE

Adjusted relative risk - the relative risks for specific cancer(s) divided by the relative risk for all cancer.

Expected rate - the anticipated number of annual deaths for a given county. Based upon national mortality rate trends shown by NCI data for 1950-1959.

Observed rate - actual number of deaths attributed to specific cancer(s) for a given county in a given time period (NCI data = 1950-1969).

Rate - annual number of deaths per 100,000 population for specific cancer(s) observed in a given time interval.

Relative risk - observed cancer mortality rate divided by expected rate based on national data, expressed as a percent (i.e., times 100).

Relative rate - cancer mortality rate for specific cancer(s) in a given county divided by the corresponding rate for the contiguous counties, expressed as a percent (i.e., times 100).

Selected cancers - refers to the sum of esophagus, stomach, bladder, liver, kidney, and pancreas cancers.

Total cancer - the sum of all cancer types.

percent higher than would be predicted from national rates and the 1.25 factor suggests that the higher risk is not attributable to generally high overall cancer rates.

9.4 CANCER MORTALITY RELATIVE TO CONTIGUOUS COUNTY LEVELS

Appendix D presents the epidemiological analysis of the 14 counties versus their contiguous counties. Included are 16 cancer classes and all cancers combined, presented according to relative rate, the normalized percentile mortality rankings, and the attributable risk. Each rate index is subdivided into male, female, and total mortality. The relative rate for the five types of cancer used in the national mortality correlations are presented in Table 9-2 for the 14 counties. The counties showing highest relative rates for all cancer are Kanahwa, West Virginia; Erie, New York; Vigo, Indiana; Harris, Texas; Warren, New Jersey; St. Clair, Illinois; and Summit, Ohio. All these counties also have high relative rates for selected cancer except St. Clair, Illinois. Washington, Alabama, had a high relative rate for selected, but low relative rate for all cancers. The counties exhibiting the highest bladder cancer rates are Erie, New York; Kanahwa, West Virginia; Salem, New Jersey; and Vigo, Indiana. It should be noted that the populations of Washington, Alabama, and St. Charles, Louisiana, are not sufficiently high to make their elevated rates very meaningful. The data on each county, presented in Appendix C, include county maps that show the county and contiguous county populations. Table 9-3 summarizes these data. Since the degree of urbanization strongly correlates with cancer mortality rates, if a county's population is greatly different from the contiguous county populations, the relia-

Table 9-2. RELATIVE RATE OF SELECTED CANCERS FOR THE THIRTEEN COUNTIES

County/state	Cancer relative rate (male/female/overall)						
	All cancer	Bladder	Esophagus	Stomach	Liver	Kidney	Pancreas
Kanahwa, W. Va.	118/111/114	156/124/144	229/134/194	93/91/91	109/83/94	121/103/112	133/129/131
Erie, N.Y.	120/107/114	127/130/127	145/109/138	121/128/123	123/109/115	112/134/118	124/115/120
Vigo, Ind.	116/108/112	138/133/136	169/99/145	106/101/104	112/88/98	87/137/104	101/127/110
Harris, Tex.	106/108/106	122/96/113	112/131/115	87/86/86	105/97/101	104/119/108	108/97/103
Warren, N.J.	105/108/106	88/123/96	127/64/117	89/95/90	97/111/104	86/117/96	106/149/123
St. Clair, Ill.	101/102/102	73/92/79	115/68/110	102/110/106	79/100/90	104/96/102	104/104/105
Salem, N. J.	98/105/100	186/123/173	92/82/92	101/86/97	83/119/101	98/113/104	112/138/122
Summit, Ohio	94/97/95	102/109/104	68/86/71	85/88/86	88/96/92	100/78/92	108/103/106
St. Charles, La.	91/99/95	81/113/88	0/271/39	63/248/116	44/45/44	44/73/56	97/71/90
St. Louis, Mo.	91/96/94	93/92/93	69/81/71	82/99/86	72/81/77	98/120/106	107/106/107
Somerset, N.J.	89/92/91	86/108/92	86/104/90	92/85/90	75/80/78	92/107/97	97/97/98
Brazoria, Tex.	87/92/90	55/106/68	87/88/89	118/125/121	93/97/95	96/64/87	105/78/98
Washington, Ala.	81/94/87	81/44/72	116/460/188	154/132/147	84/171/119	0/60/21	33/46/37

Table 9-3. SUMMARY OF POPULATION DISTRIBUTION FOR CONTIGUOUS COUNTY EVALUATION

County	County population data, 10^3 people in/contiguous counties		
	Average annual population	Total average annual pop. for contiguous counties	Range of populations of contiguous counties
Somerset, N.J.	139	1386	53-443
Vigo, Ind.	104	118	15-24
Erie, N.Y.	955	556	32-217
Kanahwa, W. Va.	229	272	12-71
Salem, Ohio	48	962	91-488
Brazoria, Tex.	66	1179	20-987
St. Charles, La.	15	236	9-179
St. Clair, Ill.	204	1484	14-652
Summit, Ohio	454	1928	44-1343
Washington, Ala.	10	275	7-197
Harris, Tex.	99	274	6-110
Warren, N.J.	63	888	10-282
St. Louis, Mo.	652	592	16-207

bility of mortality correlations is in doubt. Of the counties showing elevated rates, the following showed markedly different populations compared with their contiguous counties:

Population trend versus contiguous county

High	Low
Vigo, Ind.	Somerset, N.J.
Erie, N.Y.	Salem, N.J.
Kanahwa, W. Va.	St. Charles, La.
	Warren, N.J.
	Washington, Ala.

In counties with low relative populations, the elevated cancer rates may become more meaningful since they cannot be explained by population differences. This effect makes Salem, New Jersey, the most interesting county for bladder cancer elevation since it shows the highest relative risk (186/123) and a much lower population (48,000) than any of its contiguous counties (91,000 to 488,000). By contrast, in the counties with high populations relative to their contiguous counties, the relative risk elevations are less strongly associated with possible amine/nitrosamine exposure.

9.5 ABSOLUTE CANCER RATE COMPARISON

Table 9-4 shows cancer rates for all cancer, selected cancers, and bladder cancer.

9.6 CANCER MORTALITY RELATIVE TO NATIONAL LEVELS (RELATIVE RISK)

The disease-specific, relative risk, cancer mortality rates are summarized in Table 9-5. Adjusted relative risk levels of greater than 1.00 are shown. Relative risk values greater than 100 indicate elevations above the national rate, and adjusted relative risk values greater than 1.00

Table 9-4. ABSOLUTE CANCER RATES FOR ALL CANCERS, SELECTED CANCERS, AND BLADDER CANCER

County/ state	All cancer F/M	Bladder F/M	Esophogus F/M	Stomach F/M	Liver F/M	Kidney F/M	Pancreas F/M	Combined selected F/M
Warren, N.J.	147.6[a]/189.2[a]	3.17/7.85	0.59/5.39	7.50/14.33	6.11/4.82	2.43/3.70	8.43[a]/10.09	28.23/46.18
Salem, N.J.	146.6[a]/185.8[a]	3.62/16.08[a]	0.78/4.49	6.56/15.07	6.39/4.28	2.07/3.98	7.71/10.31	27.13/54.21
Vigo, Ind.	144.19[a]/180.76	2.88/7.09	0.82/3.02	6.81/12.71	6.68/6.37	2.92/3.54	5.77/9.37	25.94/42.10
Erie, N.Y.	142.2[a]/207.0[a]	2.95[a]/9.85[a]	0.99/6.68[a]	9.42[a]/18.80[a]	5.82[a]/5.75[a]	2.18/4.61[a]	6.09/10.49[a]	27.45/56.18
St. Clair, Ill.	138.7[a]/195.9[a]	2.41/6.24[a]	0.60/5.84[a]	7.03/13.7	6.11/4.91	2.04/4.45	5.86/10.25	24.05/45.39
Summit, Ohio	137.9[a]/185.5[a]	2.75/7.99[a]	0.86/4.40	8.15/16.15	5.85/4.85	1.67/4.12	6.12/10.42	25.40/47.93
Somerset, N.J.	135.7/182.7[a]	3.00/7.85[a]	1.13/5.17	6.61/18.10	4.65/4.50	2.37/4.31	6.03/10.46	25.80/50.39
St. Louis, Mo.	132.0/181.4[a]	2.52/7.73	0.74/3.94	6.22/11.71	5.30/4.85	2.34/4.22	5.76/10.33	22.88/42.78
Kanahwa, W. Va.	126.1/172.2	2.28/5.95	1.04/3.54	6.99/12.83[a]	6.39/6.56	2.49/3.54	6.79/10.18	25.98/42.60
Harris, Tex.	124.2/188.5[a]	2.27/7.41	1.32[a]/3.95	6.46/12.07	4.24/6.08[a]	2.05/3.71	5.72/11.13[a]	22.08/44.35
Washington, Ala.	114.0/150.6	1.15/5.84	4.66/4.63	8.22/17.43	5.93/4.51	1.14/.00	2.31/3.65	23.41/36.06
Brazoria, Tex.	114.0/165.0	2.40/4.06	1.11/3.44	8.32/14.59	4.27/5.50	1.32/3.67	4.52/11.67	21.94/42.93
St. Charles, La.	112.5/185.7	2.50/7.74	1.701/.00	15.2/9.64	2.03/2.24	1.80/1.60	3.79/11.68	27.02/32.90

[a] Indicates stastically significant elevated rates as defined by National Cancer Institute.
F/M - Female/male.

TABLE 9-5. ALL CANCER RELATIVE RISK AND RELATIVE RISK DATA FOR SELECTED CANCERS

(MALE/FEMALE)

County/ state	All cancer Relative risk	Bladder		Esophogus		Stomach	
		Rel. Risk	Adj. R. R.	Rel. Risk	Adj. R.R.	Rel. Risk	Adj. R.R.
Erie, N.Y.	120.3*/109.4*	147.8*/124.7*	1.23/1.14	164.0*/98.6	1.36/<1	125.8*/123.0*	1.05/1.12
Washington, Ala	86.1/87.7	86.9/48.5	1.01/<1	113.1/451.3	1.31/b	115.4/105.3	1.34/1.20
Kanahwa, W.Va.	101.0/97.6	90.9/96.6	<1/<1	90.9/102.1	0.90/1.05	92.8/91.1	<1/<1
Salem, N.J.	107.9/112.4*	245.8*/155.0	2.28/1.38	107.7/77.0	<1/<1	99.2/84.3	<1/<1
Harris, Tex	109.7/95.5	106.9/96.1	<1/1.01	96.9/129.7	<1/1.36	81.7/84.9	<1/<1
Somerset, N.J.	105.2/103.8	113.4/128.5	1.08/1.24	126.9/109.4	1.21/1.05	118.3/111.8	1.12/1.08
St. Charles, La	101.5/85.7	113.4/96.8	1.12/1.13	-/210.7	-/b	72.0/201.3	<1/b
St. Clair, Ill	114.1*/106.5*	93.9/102.8	<1/<1	143.9*/61.5	1.26/<1	90.2/91.7	<1/<1
St. Louis, Mo	104.0*/101.4	112.9/106.6	1.09/1.05	94.5/73.3	<1/<1	75.2/80.7	<1/<1
Brazoria, Tex	96.0/88.9	56.8/95.6	<1/1.08	77.7/140.9	<1/1.58	99.0/108.3	1.03/1.22
Vigo, Ind	103.9/109.8*	103.5/120.3	<1/1.1	75.0/81.4	<1/<1	83.7/89.0	<1/<1
Warren, N.J.	*/113.2	118.1*/141.8	1.08/1.25	133.0/59.2	1.21/<1	95.3/101.1	<1/<1
Summit, Ohio	106.6*/106.0	118.1*/117.1	1.11/1.10	107.3/85.1	1.01/<1	106.1/106.3	<1/1.00

[a] Defined as statistically high levels by the National Cancer Institute.
[b] Not frequent enough to constitute a meaningful elevation.
* Statistically significant elevation.

Table 9-5 (continued).

County/ state	Liver		Kidney		Pancreas		Selected Cancer	
	Rel. Risk	Adj. R.R.	Rel. Risk	Adj. R.R.	Rel. Risk	Adj. R.R.	Rel. Risk	Adj. R.R.
Erie, N.Y.	113.7*/109.3	<1/<1	121.6*/110.6	1.01/1.01	110.6/105.0	<1/<1	127.6/113.8	1.06/1.04
Washington, Ala	89.9/108.1	1.04/1.23	-/56.7	-/<1	36.2/39.8	<1/<1	70.5/95.2	0.82/1.08
Kanahwa, W.Va.	129.4/119.9	1.28/1.23	90.6/128.1	<1/1.31	105.7/116.8	1.05/1.20	99.2/107.8	0.98/1.10
Salem, N.J.	86.4/119.8	<1/1.07	101.2/102.0	<1/<1	110.5/130.1	1.02/1.16	122.9/111.2	1.14/0.99
Harris, Tex.	122.4*/79.6	1.12/<1	95.3/104.2	<1/1.09	116.4/99.2	1.06/1.04	100.0/91.9	0.92/0.90
Somerset, N.J.	90.6/85.4	<1/<1	111.7/117.9	<1.06/1.14	110.1/102.7	1.05/<1	112.8/105.9	1.07/1.02
St. Charles, La.	44.9/40.6	<1/<1	53.0/97.6	<1/1.14	107.1/56.1	1.05/<1	73.7/112.6	0.73/1.31
St. Clair, Ill.	97.2/114.6	<1/1.08	118.2/104.2	1.04/<1	108.8/100.3	<1/<1	103.1/99.6	0.90/0.93
St. Louis, Mo.	92.9/100.3	<1/<1	107.4/119.4	1.03/1.18	107.4/99.6	1.03/<1	96.6/95.0	0.90/0.93
Brazoria, Tex.	96.6/82.8	1.01/<1	91.3/67.5	<1/<1	126.9/75.8	1.32/<1	96.4/91.5	1.00/1.03
Vigo, Ind.	125.8/123.9	1.21/1.13	90.7/145.0	<1/1.32	98.7/99.2	<1/<1	94.7/106.3	0.91/0.97
Warren, N.J.	94.6/112.2	<1/<1	96.3/122.9	<1/1.08	105.9/140.4	<1/1.24	104.6/116.9	0.95/1.03
Summit, Ohio	95.9/109.7	<1/1.03	106.9/85.1	1.00/<1	107.0/105.6	1.00/<1	107.1/105.3	1.00/0.99

indicate specific relative risk values greater than the all cancer rate.

Potentially significant elevations of bladder cancer incidence are evaluated for aromatic amine-associated elevations, and the selected cancer values are analyzed for nitrosamine-associated elevations. All cancer values are presented for comparison purposes.

Four counties (Erie, N.Y.; Warren, N.J.; St. Clair, Ill.; and Summit, Ohio) showed statistically significant relative risk values. Three counties showed statistically significant high relative risk values for women only (Salem, N.J., and Vigo, Ind.).

Eight counties showed some elevation in bladder cancer rates. Of these, Salem, New Jersey; Erie, New York; Warren, New Jersey; Summit, Ohio; and Somerset, New Jersey, showed the greatest relative risk and adjusted relative risk elevation.

9.7 POPULATION AND INDUSTRIALIZATION DATA

Table 9-6 presents data on population density and the degree of industrialization in the 13 counties studied. The population density values reflect the population per square mile as found in the County and City Data Book. All data here are based on 1960 census figures.

The degree of industrialization is based on the number of chemical, petroleum, rubber, or plastic products manufacturing facilities in the county. The number in parentheses is the number of manufacturing facilities of any type. All data are taken from the County and City Data Book and give 1963 figures. Totals are for establishments of 20 or more employees only.

Warren, New Jersey; Salem, New Jersey; and St. Charles, Louisiana, are all shown to have low population densities

Table 9-6. FOURTEEN-COUNTY RANKING BASED ON NATIONAL AVERAGES/ALL CANCER RATES

County	All cancer rates[a]		Population density[b]	Degree of industrialization[c]
	Female	Male		
Warren, N.J.	147.640	189.201	175	8 (63)
Salem, N.J.	146.595	185.827	161	3 (23)
Vigo, Ind.	144.191	180.760	261	5 (51)
Erie, N.Y.	142.230	206.966	1006	65 (542)
St. Clair, Ill.	138.690	195.918	390	12 (92)
Summit, Ohio	137.901	185.488	1251	51 (257)
Somerset, N.J.	135.655	182.711	469	14 (85)
St. Louis, Mo.	131.979	181.411	1409	22 (224)
Kanahwa, W. Va.	126.141	172.278	279	11 (57)
Harris, Tex.	124.176	188.483	722	98 (675)
Washington,Ala.	114.009	150.645	14	2 (8)
Brazoria, Tex.	113.951	165.026	54	9 (19)
St. Charles, La.	112.541	185.711	74	4 (4)

[a] Death rate per 100,000 in county.

[b] Population per square mile, 1960 data. Ref.: County and City Data Book, 1967.

Nat'l. avg.: All cancers--129.924 (female)
172.733 (male)

[c] Industrial sites in chemical industry and total industry in parenthesis.

and low degrees of industrialization, which strengthen the argument that the bladder cancer elevations in these counties might be associated with industrial amines exposure. The relatively high population density in Summit, Ohio, and a correspondingly high industrialization result in the moderate bladder cancer elevations being relatively less meaningful.

Data for cancer incidence, population density, and degree of industrialization for the 15 areas of highest cancer mortality in the United States are presented in Table 9-7. Comparison of these data with values for the counties being investigated shows that the values for high cancer localities are in many instances orders of magnitude greater than those of the counties selected for study.

9.8 FACILITIES PRODUCING PRECURSORS FOR NITROSAMINES

Several types of industrial facilities that might be capable of contributing to the present elevated levels of aromatic amines or nitrosamines in the environment were considered in the investigation. These included a) facilities where the amines produced included secondary and tertiary amines that could react with NO_x in the atmosphere to produce nitrosamines, b) nitric acid plants that might produce relatively high concentrations of NO_x in the atmosphere to react with amines escaping from production plants, and c) facilities that used aromatic amines in production of organic dyes and pigments or in the production of rubber products. The observations from this phase of the investigation are as follows:

a) Secondary and tertiary amines production

Of the 14 test counties, five are known to contain major secondary and/or tertiary amine production facilities. It would be expected that these five

TABLE 9-7. CANCER MORTALITY RISKS FOR THE 20 HIGHEST COUNTIES NATIONALLY

(1950-1969) National ranking counties* (top 15)		All cancer		Selected cancers		Bladder cancers		Population Density $10^3/mi^2$	Degree of Industrialization
		Rate	Rel. risk	Rel. risk	Adj. rel. risk	Rel. risk	Adj. rel. risk		
1.	San Francisco CA	250.5	119.2	124.3	1.04	124.9	1.03	16.3	21 (503)
2.	City, St. Louis MO	242.5	119.5	116.3	0.97	142.8	1.19	12.3	90 (825)
3.	Philadelphia PA	226.3	124.2	122.9	0.99	136.6	1.10	15.6	120 (1812)
4.	Baltimore City MD	224.0	128.3	118.7	0.92	148.1	1.15	12.5	79 (635)
5.	N.Y. City NY	223.5	124.1	134.4	1.08	127.9	1.03	14.8	85 (5663)
6.	Suffolk MA	223.1	122.7	123.8	1.01	106.1	0.86	14.2	30 (778)
7.	Dist/Columbia DC	221.4	113.1	106.0	0.94	136.5	1.21	-	-
8.	Essex NJ	219.3	121.8	123.0	1.01	144.8	1.19	7.1	108 (953)
9.	Hudson NJ	216.9	127.7	139.7	1.09	148.4	1.16	12.9	83 (822)
10.	Ohio WV	209.6	114.7	116.0	1.01	135.2	1.18	-	-
11.	Rutland VT	206.2	113.3	105.3	0.93	147.9	1.31	-	-
12.	Ulster NY	203.6	111.7	106.0	0.95	131.4	1.18	-	-
13.	Providence RI	203.0	114.9	103.4	0.90	106.9	0.93	-	-
14.	Bucanan MO	199.8	98.6	88.2	0.91	94.2	0.96	-	-
15.	Passaic NJ	197.2	117.8	130.8	1.11	126.4	1.07	2.1	70 (632)
		Averaged Death rate per 100,000							

* High ranking Florida counties (7) omitted due to high average age.

counties might exhibit a higher than average elevation of the selected cancer types. The five counties are:

St. Charles, La. -- Union Carbide, Taft plant
Brazoria, Tex. -- Dow Chemical, Freeport plant
Vigo, Ind. -- IMC, Terre Haute plant
Erie, N.Y. -- Allied Chemical, Buffalo plant
Warren, N.J. -- J.T. Baker Chemical, Phillipsburg plant

The rate for the selected organ-specific cancers with national cancer rates show bladder cancer elevations in four of the five counties (versus eight of the 14 total) while only Vigo, Indiana, was elevated in the other screening cancers (versus three of the 14 total). The cancer rates relative to contiguous county rates showed the same four of the five counties elevated (versus nine of the 14 total and three of the five counties elevated in the other screening cancers versus six of the 14 total). Only Brazoria, Texas, did not show some elevated rates. No clear statement can be made about these relationships.

b) Amines and dye production

Dye production is of particular interest since certain aromatic dyes have long been associated with bladder cancer. The four counties of interest are:

Erie, N.Y. -- Allied Chemical, Buffalo plant
Washington, Ala. -- Ciba-Geigy, McIntosh plant
Salem, N.J. -- DuPont Chemical, Deepwater plant
Somerset, N.J. -- American Cyanamid, Bound Brook plant

The cancer elevations for these counties are more striking when compared with the national rate data (Table 9-4). Salem, New Jersey, and Erie, New York, are the two counties with the highest bladder cancer rates and Somerset, New Jersey, is also elevated. The elevations from the con-

tiguous county data (Table 9-2) are somewhat less striking; however, Salem, New Jersey, still shows by far the highest bladder cancer rate.

c) Amines and nitric acids production sites

This analysis is included since nitric acid is a precursor in nitrosamine formation. Counties containing facilities producing both of these types of compounds are

Somerset, N.J. -- American Cyanamid, Bound Brook plant
Warren, N.J. -- J.T. Baker Chemical, Phillipsburg plant
Erie, N.Y. -- Allied Chemical, Buffalo plant
St. Charles, La. -- Monsanto, Luling plant
St. Louis, Mo. -- Monsanto, St. Louis plant

Four of these five counties had elevated bladder cancer rates and Erie and St. Charles Counties showed elevations in the other cancers. Since three of these five counties were also major secondary or tertiary amine production sites, it is difficult to draw any inference from these data, except that these three sites take on added importance for further analysis. Erie, New York, is of particular interest since it contains major secondary and tertiary amine, dye manufacturing, and nitric acid plants. Additionally, Erie County contains two coke oven facilities, which could be associated with elevations in a number of cancer types.

10.0 SOURCES AND EXPOSURE ASSESSMENT OF AMINES AND NITROSAMINES

10.1 SOURCES OF AMINES AND NITROSAMINES

While the present study was aimed at identification of point sources of potential carcinogens, some thought was given to the general levels of amines and nitrosamines in the environment.

Nitrosamines and their precursors, secondary and tertiary amines, and NO_x compounds, are widely distributed in the environment; they result from both human activities and natural processes. As shown in Figure 10-1, a total environmental impact under consideration should include the following source classes for nitrosamines:

1. Industrial processes in which nitrosamines occur as a production intermediate. These compounds do not appear to be widely used; however, their use has been reported in organic chemical manufacturing, rubber processing (vulcanizing retarders and blowing agents), and rocket fuel manufacturing.[1]

2. Industrial processes in which nitrosamines occur incidentally. For example, low-molecular weight nitrosamines may be lost from complex reaction mixtures by volatility.

3. Secondary and tertiary amines sources. The manufacturing of the following processes themselves may be sources of nitrosatable amines:

   - antioxidants
   - vulcanization accelerators
   - pharmaceuticals
   - self-polishing waxes
   - synthetic detergents
   - pesticides
   - solvents
   - uranium oxide

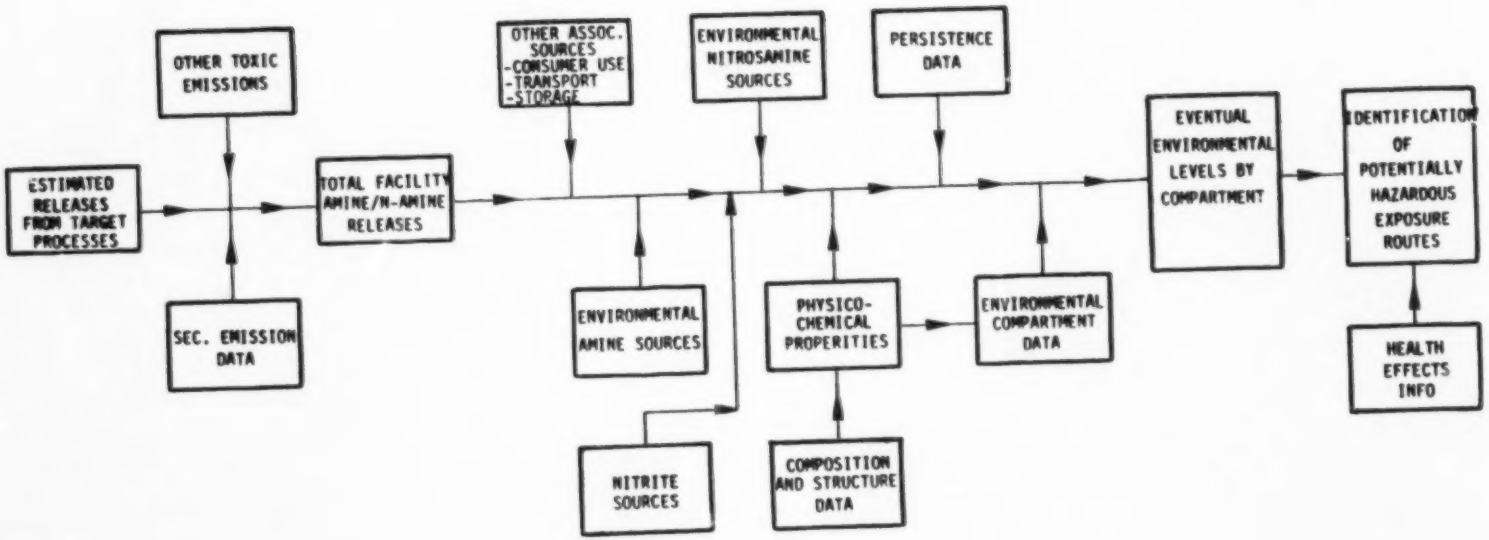


Figure 10-1. Information flow for environmental assessment of amine distribution and effects.

- wet-strength paper
- corrosion inhibitors
- animal glues
- photographic products
- leather[1]

4. Industrial operations emitting nitrosatable amines as an intermediate or by-product. Very little is known about this source class. Feedlots and rending plants are reported to emit amines from the decomposition of animal matter.[1]

5. Industrial NO_x sources. Nitrates and nitrites, precursors for nitrosamine formation are emitted primarily from motor vehicles and stationary fuel combustion sources. Only about 1 percent comes from chemical processes, mainly related to nitric acid manufacture and use.[2] Nitric acid plants are usually situated where relatively high concentrations of NO_x and amines are present at the same time.

6. Mobile sources. Motor vehicle exhaust represents a major source of NO_x; it is thought to be a source of nitrosamine, although confirmatory data are lacking.[1]

7. Emissions of other toxic materials that may have a significant health impact.

8. Other associated sources from transport, storage, or offsite amine consumption processes.

9. Environmental amine sources. These may be from other industrial sources or environmental degradation products.

10. Environmental nitrosamine sources. A wide variety of foods as well as tobacco have been found to contain N-nitrosamines.

11. Nitrite sources (the main nitrosating agent) as well as nitrate sources should be considered since they can be enzymatically reduced to nitrite by nitroreductase-containing bacteria. Of major concern in this category are nitric acid plants.

The complex source inventory given above is justified by the fact that amines in the environment have been found to be nitrosatable *in vitro* and *in vivo* (Table 10-1).

10.2 EVENTUAL ENVIRONMENTAL LEVELS

As indicated above, the sources of amines and nitrosamines in the environment are many, varied, and poorly understood. The lack of data on many elements that may affect the analysis makes it impossible to accurately predict environmental levels. Whether the impact from point sources will be discernable from background concentrations is open to question. While limited air quality data are available for analysis, there is evidence that point sources may be contributing to measurable levels of nitrosamines in the atmosphere. Table 10-2 shows measurement in the neighborhood of the Baltimore plant of FMC, where concentrations decrease with distance from the plant.

10.3 FATE AND EFFECTS ANALYSES

Figure 10-2 shows the information flow for a complete fate and effects analysis. In the present study it was impossible to test the information flow scheme proposed for identifying potentially significant amine and nitrosamine exposure routes because of limited data.

The amines that present the greatest potential impact on public health are identified by a prescreening process. The major criteria in this evaluation process are the toxicity of the amines and their degradation products, production volume, and diversity of use. The next step involves identifying the main production and consumption processes involving the "significant" amines and their corresponding industrial facilities. As shown on Figure 10-1, there are six major types of process operations that represent poten-

Reproduced from best available copy.

Table 10-1. DRUGS, PESTICIDES, AND NATURALLY OCCURRING AMINES THAT HAVE EXPERIMENTALLY PRODUCED N-NITROSO COMPOUNDS IN VIVO OR IN VITRO[3]

Compound	Class[a]	Product
Secondary amines		
Morpholine	D.P.	NO-derivative[b]
Piperazine	D	MNP.DNP
Altrazine	P	NO-derivative
Simazine	P	NO-derivative
Phenmethrazine	D	NO-derivative
Ethambutol	D	NO-derivative
Ziram	P	DMN
Thiram	P	DMN
Ferbam	P	DMN
Tertiary amines		
Aminopyrine	D	DMN
Oxytetracycline	D	DMN
Chlorpromazine	D	DMN
Dextropropozyphene	D	DMN
Chlorpheniramine	D	DMN
Methadone	D	DMN
Methapyrilene	D	DMN
Quinacrine	D	DEN
Lucanthone	D	DEN
Tolazamide	D	NO-hexamethyleneimine
Cyclizine	D	DNP
Trimethylamine	N	DMN
2-Dimethylaminoethanol	N	DMN
N,N-Dimethylgycinemethylester	-	DMN
N,N-Dimethylgycine	N	DMN
Triethanolamine	-	NO-diethanolamine
Nitrilotriacetic acid	-	NO-iminodiacetic acid
N,N-Dimethyldodecylamine	-	DMN, NO-N-methydodecylamine
Nicotine	N	NO-nornicotine
Pyribenzamine	D	NO-derivative
Carbaryl	P	NO-carbaryl
Propoxur	P	NO-propozur
Benzthiazuron	P	NO-bensthiazuron
Quaternary amines		
Tetramethylammonium chloride	-	DMN
Neurine chloride	N	DMN
Acetylcholine	N	DMN
Choline	N	DMN
Betaine	N	DMN
Carnitine	N	DMN
Trimethylamine-N-oxide	N	DMN
Tribenzylamine-N-oxide	-	Dibenzylnitrosamine

[a] D = drug, P = pesticide, and N = naturally occuring.

[b] NO-derivative of the compound nitrosated.

Table 10-2. NITROSAMINE CONCENTRATIONS IN AMBIENT AIR MEASURED IN 12 U.S. CITIES OR LOCALITIES[1]

Location	Approximate hours of sampling	Concentration range, µg/m³ (1- to 2-h peaks)		
		DMN	Unknown 1[a]	Unknown 2[a]
Baltimore, Md., area FMC property	54	1 to 36	ND[b] to 0.08	ND[b] to 2.7
Within 0.6-km radius of FMC property	27	0.03 to 7.6	ND[b] to 0.17	0.02 to 0.32
Within 0.6-to 1-km radius of FMC property	30	Trace[c] to 2.0	ND[b] to 0.03	ND[b] to 0.34
Outside 2-km radius of FMC property	14	0.02 to 0.13	0.02 to 0.04	ND[b] to 0.3
Belle, W. Va.	78	ND[b] to 0.98	ND[b] to 0.06	ND[b] to 0.08
So. Charleston and Charleston, W. Va.	30	ND[b] to 0.06		
Nitro, W. Va.	5	ND[b]		
Northern New Jersey	11	ND[b]		
Philadelphia, Pa.[d]	12	ND[e]	ND[b]	ND[b]
Wilmington, Del.[d]	12	ND[e]	ND[b]	ND[b]
Waltham, Mass.[d]	4	ND[e]	ND[b]	ND[b]
New York, N.Y.	10	ND[b] to 0.016		
Denver, Col., (Eisenhower Tunnel)	1	Trace		
Los Angeles, Cal.	1	ND[e]		
St. Louis, Mo.	1	ND[e]		

[a] Unknowns were analyzed only by the TEA technique. Total sampling time for unknowns in Baltimore, Md., was about half that for DMN and in Belle, W. Va., was about one-third that for DMN.

[b] ND = not detectable (<0.002 µg/m³).

[c] Trace is defined as a detectable but nonquantifiable amount >0.002 µg/m³.

[d] Sampled during initial TEA study only.[2]

[e] ND = not detectable (<0.1 µg/m³).

Reproduced from best available copy.

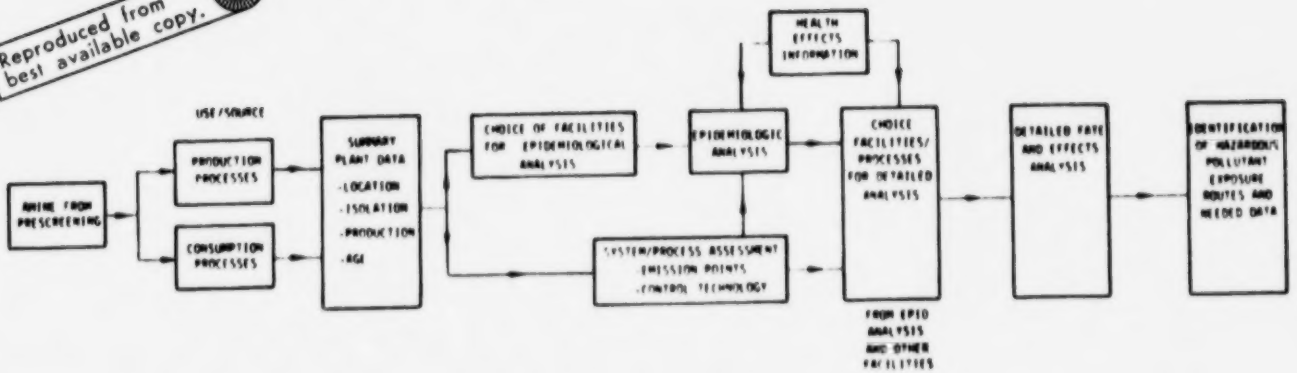


Figure 10-2. Overall information flow for amine fate and effects analysis.

tial sources of environmental release of amines. Of these, reliable data are available only for amine production processes, but even these are not assured because major amine manufacturers keep their production figures secret. Data are not systematically available for consumption processes of target amines and are very poorly defined for the remaining four sources:

1. Intermediate processes with captive amine consumption or trade-off of amines between facilities.

2. The production of a target amine as a secondary reaction product or by-product or as a contaminant in other processes.

3. The production of precursor chemicals that can form a target amine under appropriate conditions in the environment or during subsequent processing of the precursor amine.

4. Amine consumption processes for derived production. Thus even for a qualitative analysis of potential environmental exposure routes of amines or nitrosamines, detailed industrial process information about the chemical reactions involved for each is required.

Even if the process information is quite incomplete, adequate information may be available to address the following questions:

1. Does a given amine appear to represent an environmental hazard? Potentially worst plant cases are examined in this analysis.

2. Are the elevated incidences of specific forms of cancer mortality correlated with predicted exposure to certain amines, nitrites, etc.?

To address these questions, both epidemiological and plant process evaluations are needed.

The summary plant data needed include the location of plant facilities and the identification of any other industrial facilities in the vicinity that might confound health

effects and process information. The epidemiological analysis requires historical information about processes present at a given facility since the latency period for many forms of cancer is 20 to 30 years.

The purpose of this assessment is not an attempt to provide an exhaustive review of the secondary and tertiary amines industry, but to establish any causal health effects relationships. Thus, facilities are identified that would be expected to exhibit elevated cancer mortality rates in an epidemiological analysis. While the study was considered successful in identification of locations for further study, the availability of additional data would, however, have enhanced the usefulness of the report. This section discusses the types of additional data that would have been helpful.

The selection of amines for prescreening was described in Section 8.0. It is felt that the data base used for selection of the 46 chemicals was generally adequate.

10.3.1 Industrial Amines Fate Analysis Overview

This section serves as an overview, presenting a methodology for identifying the potentially significant routes of human exposure to nitrosamines and their precursor amines. This procedure, though tailored for nitrosamines, is adaptable for evaluating other potentially toxic chemical groups. The focus of the overall assessment is on the fate and effects analysis, but an epidemiological analysis is encompassed by the proposed methodology as well. Illustrative case studies are not presented, since the necessary data base was found to be generally inadequate.

10.3.2 Detailed Fate Analysis

Due to the diversity of industrially significant amines, a generalized approach is used to identify potential environmental problem areas. Figure 10-2 presents an overview of the proposed methodology for a comprehensive fate and effects assessment of areas affected by specific commercial operations. Process information would be gathered on these facilities together with other plants that show potential for environmental release of amines but have not been in operation long enough to exhibit a significant impact on the cancer mortality rate in the local population.

The epidemiological analysis attempts to correlate elevated mortality rates for specific forms of cancer with plant emissions containing amines or nitrosamines implicated with that form of cancer.

Three criteria are used to select plants for a thorough fate and effects analysis:

1. Significant elevation in cancer mortality rates as implicated by an epidemiological analysis.

2. Plants showing no elevated mortality rates from the epidemiological analysis, but containing processes that would have indicated a strong possibility of elevated mortality rates. These plants are included since it is of interest to identify those variables that may be responsible for reducing the population exposure to the target amines and/or nitrates, etc.

3. Integrated plants that have not operated long enough to be included in the epidemiological analysis.

REFERENCES

1. Environmental Protection Agency Scientific and Technical Assessment Report on Nitrosamines, EPA-600/6-77-001, U.S. EPA, Washington, D.C. June 1977.

2. Venezian, E.C. Prescreening for Environmental Hazards - A System for Selecting and Prioritizing Chemicals. EPA/560/1-77/002, U.S. EPA, Washington, D.C. April 1977.

3. Mirvish, S.S. FOrmation of N-nitroso Compounds: Chemistry, Kinetics and In Vivo Occurrence. Tox. and Appl. Pharmacol. 31, 1975.

4. NATO Control Techniques for Nitorgen Oxides Emissions from Stationary Sources. Burssels, Belgium. October 1973.

5. Montesano, R. and H. Bartsch. Mutagenic and Carcinogenic N-Nitrose Compounds: Possible Environmental Hazards. Mutation Research, 32: 179-228, 1976.